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(54) Title: NOVEL SURFACE PROTEIN OF *NEISSERIA MENINGITIDIS*

(57) Abstract

The invention provides a novel surface polypeptide from *Neisseria meningitidis* as well as nucleic acid and nucleic acid sequence homologues encoding this protein. Pharmaceutical compositions containing the polypeptide and nucleic acids of the invention are also disclosed as well as methods useful in the treatment, prevention and diagnosis of *N. meningitidis* infection.

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TITLE

"NOVEL SURFACE ANTIGEN"

FIELD OF THE INVENTION

The present invention relates to novel polypeptides as for example obtainable from *Neisseria meningitidis*, to nucleotide sequences encoding such polypeptides, to the use of these in diagnostics, in therapeutic and prophylactic vaccines and in the design and/or screening of medicaments.

BACKGROUND OF THE INVENTION

Neisseria meningitidis is a Gram-negative bacterium and the causative agent of meningococcal meningitis and septicemia. Its only known host is the human, and it may be carried asymptomatically by approximately 10% of the population (Caugant, D. *et al*, 1994, *Journal of Clinical Microbiology*, **32**:323-30).

N. meningitidis may express a polysaccharide capsule, and this allows classification of the bacteria according to the nature of the capsule expressed. There are at least thirteen serogroups of *N. meningitidis*: A,B,C,29-E,H,I,K,L,W135,X,Y and Z, of which serogroups A, B, and C cause 90% of meningococcal disease (Poolman, J.T. *et al*, 1995, *Infectious Agents and Disease*, **4**:13-28). Vaccines directed against serogroups A and C are available, but the serogroup B capsular polysaccharide is poorly immunogenic and does not induce protection in humans.

Other membrane and extracellular components are therefore being examined for their suitability for

inclusion in vaccines. Examples include the outer membrane proteins of classes 1, 2 and 3 (porins), and classes 4 (Rmp) and 5 (Opacity proteins). However, to date, none of these candidates is able to induce complete protection, particularly in children (Romero, J.D., 1994, *Clinical Microbiology Review,* 7:559-575; Poolman, J.T. *et al*, 1995, *supra*).

To create an effective vaccine, it is necessary to identify components of *N. meningitidis* which are present in a majority of strains, and which are capable of inducing a protective immune response (bactericidal antibodies). In this regard, reference may be made to Brodeur *et al.* (International Publication WO 96/29412) who disclose a 22 kDa surface protein which is highly conserved across 99% of all known strains of *N. meningitidis*. Injection of purified recombinant 22 kDa surface protein protected 80% of immunized mice against development of a lethal infection by *N. meningitidis*. Notwithstanding the discovery of this protein, there is still a need to isolate more surface proteins of *N. meningitidis* which are highly conserved across a plurality of strains, and which have immuno-protective profiles against *N. meningitidis*, and/or which may be used in combination with other components of *N. meningitidis* to enhance the efficacy of protection against this organism.

SUMMARY OF THE INVENTION

The present inventors have discovered a new gene which is present in all tested strains of *N. meningitidis* and which encodes a novel polypeptide having a predicted molecular weight of about 62 kDa. Based upon its sequence characteristics and homologies, this polypeptide is predicted to be an

adhesin and this, together with experimental data suggests that it constitutes a surface protein which may be useful for the production of therapeutic and/or prophylactic vaccines against *N. meningitidis* as described hereinafter.

Accordingly, in one aspect of the invention, there is provided an isolated polypeptide or fragment thereof, or variant or derivative of these, said polypeptide selected from the group consisting of:

(a) a polypeptide according to SEQ ID NO 2;
(b) a polypeptide according to SEQ ID NO 5;
(c) a polypeptide according to SEQ ID NO 7;
(d) a polypeptide according to SEQ ID NO 9;
(e) a polypeptide according to SEQ ID NO 11;
(f) a polypeptide according to SEQ ID NO 13;
(g) a polypeptide according to SEQ ID NO 15;
(h) a polypeptide according to SEQ ID NO 17;
(i) a polypeptide according to SEQ ID NO 19; and
(j) a polypeptide according to SEQ ID NO 21.

Preferably, said polypeptide, fragment, variant or derivative displays immunological activity against one or more members selected from the group consisting of:-

(i) *N. meningitidis*;
(ii) said polypeptide;
(iii) said fragment;
(iv) said variant; and
(v) said derivative;

According to another aspect, the invention provides an isolated nucleic acid sequence encoding a polypeptide or fragment thereof, or variant or derivative of said fragment or polypeptide, according to the first-mentioned aspect. Suitably, said sequence is selected from the group consisting of:

(1) the nucleotide sequence of SEQ ID NO 1;
(2) the nucleotide sequence of SEQ ID NO 3;
(3) the nucleotide sequence of SEQ ID NO 4;
(4) the nucleotide sequence of SEQ ID NO 6;
(5) the nucleotide sequence of SEQ ID NO 8;
(6) the nucleotide sequence of SEQ ID NO 10;
(7) the nucleotide sequence of SEQ ID NO 12;
(8) the nucleotide sequence of SEQ ID NO 14;
(9) the nucleotide sequence of SEQ ID NO 16;
(10) the nucleotide sequence of SEQ ID NO 18;
(11) the nucleotide sequence of SEQ ID NO 20;
(12) a nucleotide sequence fragment of any one of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 20; and
(13) a nucleotide sequence homologue of any of the foregoing sequences

Preferably, said sequences encode a product displaying immunological activity against one or more members selected from the group consisting of:-

(i) *N. meningitidis;*
(ii) said polypeptide of the first-mentioned aspect;
(iii) said fragment of said first-mentioned aspect;
(iv) said variant of said first-mentioned aspect; and
(v) said derivative of said first-mentioned aspect.

In yet another aspect, the invention resides in an expression vector comprising a nucleic acid sequence according to the second-mentioned aspect wherein said sequence is operably linked to transcriptional and translational regulatory nucleic acid.

In a further aspect, the invention provides a host cell containing an expression vector according to the third-mentioned aspect.

In yet a further aspect of the invention, there is provided a method of producing a recombinant polypeptide according to the first-mentioned aspect, said method comprising the steps of:

(A) culturing a host cell containing an expression vector according to the third-mentioned aspect such that said recombinant polypeptide is expressed from said nucleic acid; and

(B) isolating said recombinant polypeptide.

In a still further aspect, the invention provides an antibody or fragment thereof that binds to one or more members selected from the group consisting of:-

(1) *N. meningitidis;*

(2) said polypeptide of the first-mentioned aspect;

(3) said fragment of the first-mentioned aspect;

(4) said variant of the first-mentioned aspect; and

(5) said derivative of the first-mentioned aspect.

In yet another aspect, the invention provides a method of detecting *N. meningitidis* in a biological

sample suspected of containing same, said method comprising the steps of:-

(A) isolating the biological sample from a patient;

(B) mixing the above-mentioned antibody or fragment with the biological sample to form a mixture; and

(C) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence of *N. meningitidis*.

According to a further aspect, there is provided a method of detecting *N. meningitidis* bacteria in a biological sample suspected of containing said bacteria, said method comprising the steps of:-

(I) isolating the biological sample from a patient;

(II) detecting a nucleic acid sequence according to the second-mentioned aspect in said sample which indicates the presence of said bacteria.

The invention further contemplates a method for diagnosing infection of patients by *N. meningitidis*, said method comprising the steps of:-

(1) contacting a biological sample from a patient with a polypeptide, fragment, variant or derivative of the invention; and

(2) determining the presence or absence of a complex between said polypeptide, fragment, variant or derivative and *N. meningitidis*-specific antibodies in said sample, wherein the presence of

said complex is indicative of said infection.

The invention also extends to the use of the polypeptide according to the first-mentioned aspect, the use of the nucleic acids according to the second-mentioned aspect or the use of the antibody or antibody fragment mentioned above in a kit for detecting *N. meningitidis* bacteria in a biological sample.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising an isolated polypeptide or fragment thereof, or a variant or derivative of these, according to the first mentioned aspect.

Preferably, said pharmaceutical composition is a vaccine.

In yet a further aspect, the invention provides a method of preventing infection of a patient by *N. meningitidis*, comprising the step of administrating a pharmaceutically effective amount of the above-mentioned vaccine.

In a further aspect, the invention provides a method of identifying an immunoreactive fragment of a polypeptide, variant or derivatives according to the first mentioned aspect, comprising the steps of:-

(a) generating a fragment of said polypeptide, variant or derivative;

(b) administering said fragment to a mammal; and

(c) detecting an immune response in said mammal which response includes production of elements which specifically bind *N. meningitidis* and/or said polypeptide, variant or

derivative, and/or a protective effect against *N. meningitidis* infection.

BRIEF DESCRIPTION OF THE DRAWINGS

"FIG. 1 depicts plasmid maps and cloning strategy. Primers A3A and A3B (SEQ ID NOS 28 and 29, respectively) were used to amplify from MC58 the region identified in the TIGR database as a homologue of AIDA-I". PCR product was cloned to give pNMAIDA3. Primers A3C (SEQ ID NO 30) and A3D (SEQ ID NO 31) were used in inverse PCR to amplify a 3kbp EagI fragment encompassing *hiaNm*. This product was cloned to give piEAGA3. piEAGA3 was subcloned to give piEagA3.8 and piEagA3.9. Primers HiaNm:M and HiaNm:P (SEQ ID NOS 22 and 23, respectively) were used to amplify the contiguous region from MC58 and the product cloned to create pHiaNm. Primers Hia-MBPA (SEQ ID NO 24) and Hia-MBPB (SEQ ID NO 25) were used to amplify the open reading frame of *hiaNm*, and the product was cloned into pMALC2 to create pMBP-HiaNm;

FIG. 2 is a Southern blot of genomic DNA of a number of strains of *N. meningitidis*. 2A: serogroup B strains. Lane 1 PMC28, Lane 2 PMC27, Lane 3 PMC25, Lane 4 PMC24, Lane 5 PMC16, Lane 6 PMC13, Lane 7 PMC12, Lane 8 MWt standards, Lane 9 2970, Lane 10 1000, Lane 11 528 Lane 12 SWZ107, Lane 13 H41, Lane 14 H38, Lane 15 NGH36, Lane 16 H15, Lane 17 NGG40, Lane 18 NGF26, Lane 19 NGE30, Lane 20 Lane NGE28 2B: Strains of serogroups other than B. Lane 1 PMC3, Lane 2 PMC17, Lane 3 PMC20, Lane 4 PMC23, Lane 5 PMC8, Lane 6 PMC9, Lane 7 PMC11, Lane 8 PMC14, Lane 9 PMC18, Lane 10 PMC21, Lane 11 PMC29, Lane 12 MWt standards, Lane 13 PMC19, Lane 14 PMC1, Lane 15 PMC6, Lane 16 PMC10, Lane 17 PMC22, Lane 18 PMC26, Lane 19 PMC2. Molecular

weight markers indicated in kilobase pairs (kb). Genomic DNA was hybridized with a probe corresponding to ntp 276-2054 of SEQ ID NO 1;

FIG. 3 shows a Coomassie stained gel of MBP-HiaNm. Cells containing pMALC2 (Lane 2) or pMBP-HiaNm (Lane 3) after induction with IPTG. Lane 1 molecular weight standards (kDa). Arrows indicate MBP and MBP-HiaNm;

FIG. 4 is a western blot of MC58 and MC58ΔHiaNm proteins incubated with rabbit immune sera. Lane 1; molecular weight standards indicated in kDa, Lane 2 total cellular protein of MC58, Lane 3 total cellular protein of MC58ΔHiaNm Lane 4, OMC preparation of MC58, Lane 5 OMC preparation of MC58ΔHiaNm, each lane contained 50 μL of protein suspension of A_{280}= 3.75;

FIG. 5 shows a Coomassie stained gel run in parallel to the gel that was Western blotted in FIG 4. Lanes are the same as for FIG 4;

FIG. 6 shows a sequence comparison of polypeptides of HiaNm, Hia, Hsf using the PILEUP alignment program; and

FIG. 7 shows a sequence comparison of polypeptide sequences of HiaNm from 10 strains of *N. meningitidis* using the PILEUP program

DETAILED DESCRIPTION OF THE INVENTION

Throughout this specification and the appendant claims, unless the context requires otherwise, the words "comprise", "comprises" and "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Polypeptide sequences

The present invention provides an isolated polypeptide according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21, or fragment respectively thereof, or variant or derivative of these. In a preferred embodiment, the polypeptide, fragments, variants and derivatives of the invention display immunological activity against any one member selected from the group consisting of *N. meningitidis*, said polypeptide, said fragment, said variant and said derivative.

SEQ ID NO 2 corresponds to the novel about 62 kDa surface polypeptide of the *hiaNm* gene obtained from *N. meningitidis* strain MC58, as described more fully hereinafter. SEQ ID NOS 5, 7, 9, 11, 13, 15, 17, 19, and 21 correspond to homologous polypeptides deduced from nucleotide sequences obtained from *N. meningitidis* strains BZ10, BZ198, EG327, EG329, H15, H38, H41, P20, and PMC21, respectively.

For the purposes of this invention, the term *"immunological activity"* refers to the ability of the aforementioned polypeptide, fragment, variant or derivative to produce an immune response in a mammal to which it is administered, wherein the response includes the production of elements which specifically bind *N. meningitidis* and/or said polypeptide, fragment, variant or derivative, and/or a protective effect against *N. meningitidis* infection.

By *"isolated"* is meant material which is substantially or essentially free from components which normally accompany it in its native state.

By *"polypeptide"* is meant long chain peptides including proteins.

As used herein, the term *"fragment"* includes deletion mutants and small peptides, for example of at least 6, preferably at least 10 and more preferably at least 20 amino acids in length, which comprise antigenic determinants or epitopes. Several such fragments may be joined together. Peptides of this type may be obtained through the application of standard recombinant nucleic acid techniques or synthesized using conventional liquid or solid phase synthesis techniques. For example, reference may be made to solution synthesis or solid phase synthesis as described, for example, in Chapter 9 entitled *"Peptide Synthesis"* by Atherton and Shephard which is included in a publication entitled *"Synthetic Vaccines"* edited by Nicholson and published by Blackwell Scientific Publications. Alternatively, peptides can be produced by digestion of a polypeptide of the invention with proteinases such as endoLys-C, endoArg-C, endoGlu-C and staphylococcins V8-protease. The digested fragments can be purified by, for example, high performance liquid chromatographic (HPLC) techniques.

The term *"variant"* refers to polypeptides in which one or more amino acids have been replaced by different amino acids. It is well understood in the art that some amino acids may be changed to others with broadly similar properties without changing the nature of the activity of the polypeptide (conservative substitutions). Exemplary conservative substitutions in the polypeptide may be made according to the following table:

TABLE 1

Original Residue	Exemplary Substitutions
Ala	Ser

Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile,
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

Substantial changes in function are made by selecting substitutions that are less conservative than those shown in TABLE 1. Other replacements would be non-conservative substitutions and relatively fewer of these may be tolerated. Generally, the substitutions which are likely to produce the greatest changes in a polypeptide's properties are those in which (a) a hydrophilic residue (*e.g.*, Ser or Thr) is substituted for, or by, a hydrophobic residue (*e.g.*, Ala, Leu, Ile, Phe or Val); (b) a cysteine or proline is substituted for, or by, any other residue; (c) a residue having an electropositive side chain (*e.g.*, Arg, His or Lys) is substituted for, or by, an electronegative residue (*e.g.*, Glu or Asp) or (d) a residue having a bulky side chain (*e.g.*, Phe or Trp) is substituted for, or by, one having a smaller side chain (*e.g.*, Ala, Ser)or no side chain (*e.g.*, Gly).

In general, variants will be at least 75% homologous, more suitably at least 80%, preferably at least 85%, and most preferably at least 90% homologous to the basic sequences as for example shown in SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21. Homology is defined as the percentage number of amino acids which are identical or constitute conservative substitutions as defined in Table 1. Homology may be determined using sequence comparison programs such as GAP (Deveraux *et al.* 1984, *Nucleic Acids Research* **12**, 387-395) which is incorporated herein by reference. In this way sequences of a similar or substantially different length to those cited herein may be compared by insertion of gaps into the alignment, such gaps being determined, for example, by the comparison algorithm used by GAP. What constitutes suitable variants may be determined by conventional techniques. For example, nucleic acids encoding polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 can be mutated using either random mutagenesis for example using transposon mutagenesis, or site-directed mutagenesis. The resultant DNA fragments are then cloned into suitable expression hosts such as *E. coli* using conventional technology and clones which retain the desired activity are detected. Where the clones have been derived using random mutagenesis techniques, positive clones would have to be sequenced in order to detect the mutation. The term *"variant"* also includes naturally occurring allelic variants.

By *"derivative"* is meant a polypeptide which has been derived from the basic sequence by modification, for example by conjugation or complexing with other chemical moieties or by post-translational modification techniques as would be understood in the

art. Such derivatives include amino acid deletions and/or additions to polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 or variants thereof wherein said derivatives retain immunological activity. *"Additions"* of amino acids may include fusion of the polypeptides or variants thereof with other polypeptides or proteins. In this regard, it will be appreciated that the polypeptides or variants of the invention may be incorporated into larger polypeptides, and such larger polypeptides may also be expected to retain immunological activity against, for example, *N. meningitidis*. The polypeptides as described above may be fused to a further protein, for example, which is not derived from *N. meningitidis*. The other protein may, by way of example, assist in the purification of the protein. For instance a polyhistidine tag, or a maltose binding protein may be used in this respect as described in more detail below. Alternatively, it may produce an immune response which is effective against *N. meningitidis* or it may produce an immune response against another pathogen. Other possible fusion proteins are those which produce an immunomodulatory response. Particular examples of such proteins include Protein A or glutathione S-transferase (GST). In addition, the polypeptide may be fused to an oligosaccharide based vaccine component where it acts as a carrier protein.

Other derivatives contemplated by the invention include, but are not limited to, modification to side chains, incorporation of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the polypeptides, fragments and variants of the invention.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by acylation with acetic anhydride; acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; amidination with methylacetimidate; carbamoylation of amino groups with cyanate; pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$; reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$; and trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS).

The carboxyl group may be modified by carbodiimide activation via O-acylisourea formation followed by subsequent derivitization, by way of example, to a corresponding amide.

The guanidine group of arginine residues may be modified by formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

Sulphydryl groups may be modified by methods such as performic acid oxidation to cysteic acid; formation of mercurial derivatives using 4-chloromercuriphenylsulphonic acid, 4-chloromercuribenzoate;2-chloromercuri-4-nitrophenol, phenylmercury chloride, and other mercurials; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; carboxymethylation with iodoacetic acid or iodoacetamide; and carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified, for example, by alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphonyl halides or by oxidation with N-bromosuccinimide.

Tyrosine residues, may be modified by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

The imidazole ring of a histidine residue may be modified by N-carbethoxylation with diethylpyrocarbonate or by alkylation with iodoacetic acid derivatives.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include but are not limited to, use of 4-amino butyric acid, 6-aminohexanoic acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 4-amino-3-hydroxy-6-methylheptanoic acid, t-butylglycine, norleucine, norvaline, phenylglycine, ornithine, sarcosine, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acids contemplated by the present invention is shown in TABLE 2.

TABLE 2

Non-conventional amino acid	Non-conventional amino acid
α-aminobutyric acid	L-N-methylalanine
α-amino-α-methylbutyrate	L-N-methylarginine
aminocyclopropane-carboxylate	L-N-methylasparagine
aminoisobutyric acid	L-N-methylaspartic acid
aminonorbornyl-carboxylate	L-N-methylcysteine
cyclohexylalanine	L-N-methylglutamine
cyclopentylalanine	L-N-methylglutamic acid
L-N-methylisoleucine	L-N-methylhistidine
D-alanine	L-N-methylleucine
D-arginine	L-N-methyllysine
D-aspartic acid	L-N-methylmethionine
D-cysteine	L-N-methylnorleucine
D-glutamate	L-N-methylnorvaline
D-glutamic acid	L-N-methylornithine
D-histidine	L-N-methylphenylalanine
D-isoleucine	L-N-methylproline
D-leucine	L-N-medlylserine

D-lysine	L-N-methylthreonine
D-methionine	L-N-methyltryptophan
D-ornithine	L-N-methyltyrosine
D-phenylalanine	L-N-methylvaline
D-proline	L-N-methylethylglycine
D-serine	L-N-methyl-t-butylglycine
D-threonine	L-norleucine
D-tryptophan	L-norvaline
D-tyrosine	α-methyl-aminoisobutyrate
D-valine	α-methyl-γ-aminobutyrate
D-α-methylalanine	α-methylcyclohexylalanine
D-α-methylarginine	α-methylcylcopentylalanine
D-α-methylasparagine	α-methyl-α-napthylalanine
D-α-methylaspartate	α-methylpenicillamine
D-α-methylcysteine	N-(4-aminobutyl)glycine
D-α-methylglutamine	N-(2-aminoethyl)glycine
D-α-methylhistidine	N-(3-aminopropyl)glycine
D-α-methylisoleucine	N-amino-α-methylbutyrate
D-α-methylleucine	α-napthylalanine
D-α-methyllysine	N-benzylglycine
D-α-methylmethionine	N-(2-carbamylediyl)glycine
D-α-methylornithiine	N-(carbamylmethyl)glycine
D-α-methylphenylalanine	N-(2-carboxyethyl)glycine
D-α-methylproline	N-(carboxymethyl)glycine
D-α-methylserine	N-cyclobutylglycine
D-α-methylthreonine	N-cycloheptylglycine
D-α-methyltryptophan	N-cyclohexylglycine
D-α-methyltyrosine	N-cyclodecylglycine
L-α-methylleucine	L-α-methyllysine
L-α-methylmethionine	L-α-methylnorleucine
L-α-methylnorvatine	L-α-methylornithine
L-α-methylphenylalanine	L-α-methylproline
L-α-methylserine	L-α-methylthreonine
L-α-methyltryptophan	L-α-methyltyrosine
L-α-methylvaline	L-N-methylhomophenylalanine
N-(N-(2,2-diphenylethyl	N-(N-(3,3-diphenylpropyl

carbamylmethyl)glycine 1-carboxy-1-(2,2-diphenyl-ethyl amino)cyclopropane	carbamylmethyl)glycine

The invention also contemplates covalently modifying a polypeptide, fragment or variant of the invention with dinitrophenol, in order to render it immunogenic in humans

Preferably the invention comprises a polypeptide selected from any one of the polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Polypeptides of the inventions may be prepared by any suitable procedure known to those of skill in the art. For example, the polypeptides may be prepared by a procedure including the steps of:

(a) preparing a recombinant nucleic acid containing a nucleotide sequence encoding a polypeptide according to any one of SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21, or fragment thereof, or variant or derivative of these, which nucleotide sequence is operably linked to transcriptional and translational regulatory nucleic acid;

(b) transfecting or transforming a suitable host cell with the recombinant nucleic acid;

(c) culturing the host cell to express recombinant polypeptide from said recombinant nucleic acid; and

(d) isolating the recombinant polypeptide.

Suitably said nucleotide sequence is selected from the group consisting of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16 ,18 and 20.

By *"recombinant polypeptide"* is meant a polypeptide made using recombinant techniques, *i.e.*, through the expression of a recombinant nucleic acid.

The term *"recombinant nucleic acid"* as used herein refers to nucleic acid formed *in vitro* by the manipulation of nucleic acid into a form not normally found in nature. In this regard, the recombinant nucleic acid preferably comprises an expression vector which may be either a self-replicating extra-chromosomal vector such as a plasmid, or a vector which integrates into a host genome. Generally, such expression vectors include transcriptional and translational regulatory nucleic acid operably linked to the said nucleotide sequence.

By *"operably linked"* is meant that the transcriptional and translational regulatory nucleic acid is positioned relative to the nucleotide sequence encoding the said polypeptide, fragment, variant or derivative in such a manner that such transcription is initiatable. The transcriptional and translational regulatory nucleic acid will generally be appropriate for the host cell used for expression. Numerous types of appropriate expression vectors, and suitable regulatory sequences are known in the art for a variety of host cells.

Typically, the transcriptional and translational regulatory nucleic acid may include, but is not limited to, promoter sequences, leader or signal sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences.

Constitutive or inducible promoters as known in the art are contemplated by the invention. The promoters may be either naturally occurring promoters, or hybrid promoters which combine elements of more than one promoter.

In a preferred embodiment, the expression vector contains a selectable marker gene to allow the selection of transformed host cells. Selection genes are well known in the art and will vary with the host cell used.

The expression vector may also include a fusion partner (typically provided by the expression vector) so that the recombinant polypeptide of the invention is expressed as a fusion polypeptide with said fusion partner. The main advantage of fusion partners is that they assist identification and/or purification of said fusion polypeptide.

In order to express said fusion polypeptide, it is necessary to ligate a nucleotide sequence according to the invention into the expression vector so that the translational reading frames of the fusion partner and the nucleotide sequence of the invention coincide.

Well known examples of fusion partners include, but are not limited to, glutathione-S-transferase (GST), Fc potion of human IgG, maltose binding protein (MBP) and hexahistidine (HIS_6), which are particularly useful for isolation of the fusion polypeptide by affinity chromatography. For the purposes of fusion polypeptide purification by affinity chromatography, relevant matrices for affinity chromatography are glutathione-, amylose-, and nickel- or cobalt-conjugated resins respectively. Many such matrices are available in "kit" form, such as the QIAexpress™ system (Qiagen) useful with (HIS_6) fusion partners and the Pharmacia GST purification system.

Another fusion partner well known in the art is green fluorescent protein (GFP). This fusion partner serves as a fluorescent "tag" which allows the

fusion polypeptide of the invention to be identified by fluorescence microscopy or by flow cytometry. The GFP tag is useful when assessing subcellular localization of the fusion polypeptide of the invention, or for isolating cells which express the fusion polypeptide of the invention. Flow cytometric methods such as fluorescence activated cell sorting (FACS) are particularly useful in this latter application.

Preferably, the fusion partners also have protease cleavage sites, such as for Factor X_a or Thrombin, which allow the relevant protease to partially digest the fusion polypeptide of the invention and thereby liberate the recombinant polypeptide of the invention therefrom. The liberated polypeptide can then be isolated from the fusion partner by subsequent chromatographic separation.

Fusion partners according to the invention also include within their scope "epitope tags", which are usually short peptide sequences for which a specific antibody is available. Well known examples of epitope tags for which specific monoclonal antibodies are readily available include c-myc, influenza virus haemagglutinin and FLAG tags.

Recombinant polypeptides of the invention may be produced by culturing a host cell transformed with an expression vector containing nucleic acid encoding a polypeptide, fragment, variant or derivative according to the invention. The conditions appropriate for protein expression will vary with the choice of expression vector and the host cell. This is easily ascertained by one skilled in the art through routine experimentation.

Suitable host cells for expression may be prokaryotic or eukaryotic. One preferred host cell

for expression of a polypeptide according to the invention is a bacterium. The bacterium used may be *Escherichia coli*. Alternatively, the host cell may be an insect cell such as, for example, *SF9* cells which may be utilized with a baculovirus expression system.

The recombinant protein may be conveniently prepared by a person skilled in the art using standard protocols as for example described in Sambrook, *et al.*, MOLECULAR CLONING. A LABORATORY MANUAL (Cold Spring Harbor Press, 1989), incorporated herein by reference, in particular Sections 16 and 17; Ausubel *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (John Wiley & Sons, Inc. 1994-1998), incorporated herein by reference, in particular Chapters 10 and 16; and Coligan *et al.*, CURRENT PROTOCOLS IN PROTEIN SCIENCE (John Wiley & Sons, Inc. 1995-1997) which is incorporated by reference herein, in particular Chapters 1, 5 and 6.

Nucleotide sequences

The invention further provides a nucleotide sequence which encodes a polypeptide, fragment, variant or derivative as defined above. Suitably said sequence is selected from the group consisting of:- SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16 ,18 and 20; a nucleotide sequence fragment of any one of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 20; and a nucleotide sequence homologue of the foregoing sequences. Preferably, these sequences encode a product displaying immunological activity as defined above.

As will be more fully described hereinafter, SEQ ID NO 1 corresponds to the *hiaNm* gene obtained from *N. meningitidis* strain MC58. This gene encodes

the novel 62 kDa (approximately) surface polypeptide of SEQ ID NO 2. SEQ ID NO 3 corresponds to the *hiaNm* open reading frame sequence of strain MC58, HiaNm. SEQ ID NOS 4, 6, 8, 10, 12, 14, 16, 18, and 20 correspond to the homologous *hiaNm* open reading frame sequences obtained from *N. meningitidis* strains BZ10, BZ198, EG327, EG329, H15, H38, H41, P20, and PMC21, respectively.

The term *"nucleotide sequence"* as used herein designates mRNA, RNA, cRNA, cDNA or DNA.

The term *"nucleotide sequence homologues"* generally refers to nucleotide sequences which hybridize with a wild-type nucleotide sequence according to the invention under substantially stringent conditions. Suitable hybridization conditions will be discussed hereinafter.

The nucleotide sequence homologues of the invention may be prepared according to the following procedure:

(i) obtaining a nucleic acid extract from a suitable host;

(ii) creating primers which are optionally degenerate wherein each comprises a portion of a wild-type nucleotide sequence of the invention; and

(iii) using said primers to amplify, via nucleic acid amplification techniques, one or more amplification products from said nucleic acid extract.

Suitably, the host may be a bacterium. Preferably, the host is from the genus *Neisseria*, more preferably from *N. meningitidis*.

Preferably, the primers are selected from the group consisting of:-

(1) 5'-TTAGATTCCACGTCCCAGATT-3' (SEQ ID NO 22);

(2) 5'-CTTCCCTTCAAACCTTCC-3' (SEQ ID NO 23);

(3) 5'-GGTCGCGGATCCATGAACAAAATATACCGCAT-3' (SEQ ID NO 24);

(4) 5'-TCACCCAAGCTTAAGCCCTTACCACTGATAAC-3' (SEQ ID NO 25);

(5) 5'-CCAAACCCCGATTTAACC-3' (SEQ ID NO 26);

(6) 5'-AATCGCCACCCTTCCCTTC-3' (SEQ ID NO 27);

(7) 5'-TTTGCAACGGTTCAGGCA-3' (SEQ ID NO 28);

(8) 5'-TATTCAGCAGCGTATCGG-3' (SEQ ID NO 29);

(9) 5'-TGCCTGAACCGTTGCAAA-3' (SEQ ID NO 30); and

(10) 5'-CCGATACGCTGCTGAATA-3' (SEQ ID NO 31).

Suitable nucleic acid amplification techniques are well known to the skilled addressee, and include polymerase chain reaction (PCR) as for example described in Ausubel *et al.* (1994-1998, *supra*, Chapter 15) which is incorporated herein by reference; strand displacement amplification (SDA) as for example described in U.S. Patent No 5,422,252 which is incorporated herein by reference; rolling circle replication (RCR) as for example described in Liu *et al.*, (1996, *J. Am. Chem. Soc.* **118**:1587-1594 and International application WO 92/01813) and Lizardi *et al.*, (International Application WO 97/19193) which are

incorporated herein by reference; nucleic acid sequence-based amplification (NASBA) as for example described by Sooknanan *et al.*, (1994, *Biotechniques* **17**:1077-1080) which is incorporated herein by reference; and Q-β replicase amplification as for example described by Tyagi *et al.*, (1996, *Proc. Natl. Acad. Sci. USA* **93**:5395-5400) which is incorporated herein by reference.

As used herein, an *"amplification product"* refers to a nucleic acid product generated by nucleic acid amplification techniques.

"Hybridize" or *"hybridization"* is used here to denote the pairing of complementary bases of distinct nucleotide sequences to produce a DNA-DNA hybrid, a DNA-RNA hybrid, or an RNA-RNA hybrid according to base-pairing rules.

In DNA, complementary bases are:

(i) A and T; and

(ii) C and G.

In RNA, complementary bases are:

(i) A and U; and

(ii) C and G.

In RNA-DNA hybrids, complementary bases are:

(i) A and U;

(ii) A and T; and

(iii) G and C.

Typically, substantially complementary nucleotide sequences are identified by blotting techniques that include a step whereby nucleotides are immobilized on a matrix (preferably a synthetic membrane such as nitrocellulose), a hybridization step, and a detection step. Southern blotting is used to identify a complementary DNA sequence; northern blotting is used to identify a complementary RNA

sequence. Dot blotting and slot blotting can be used to identify complementary DNA/DNA, DNA/RNA or RNA/RNA polynucleotide sequences. Such techniques are well known by those skilled in the art, and have been described in Ausubel *et al.* (1994-1998, *supra*) at pages 2.9.1 through 2.9.20.

According to such methods, Southern blotting involves separating DNA molecules according to size by gel electrophoresis, transferring the size-separated DNA to a synthetic membrane, and hybridizing the membrane bound DNA to a complementary nucleotide sequence labeled radioactively, enzymatically or fluorochromatically. In dot blotting and slot blotting, DNA samples are directly applied to a synthetic membrane prior to hybridization as above.

An alternative blotting step is used when identifying complementary nucleotide sequences in a cDNA or genomic DNA library, such as through the process of plaque or colony hybridization. A typical example of this procedure is described in Sambrook *et al.*, (1989, *supra*) Chapters 8-12.

Typically, the following general procedure can be used to determine hybridization conditions. Nucleotide sequences are blotted/transferred to a synthetic membrane, as described above. A wild type nucleotide sequence of the invention is labeled as described above, and the ability of this labeled nucleotide sequence to hybridize with an immobilized nucleotide sequence analyzed.

A skilled addressee will recognize that a number of factors influence hybridization. The specific activity of radioactively labeled polynucleotide sequence should typically be greater than or equal to about 10^8 dpm/mg to provide a detectable signal. A radiolabeled nucleotide sequence

of specific activity 10^8 to 10^9 dpm/mg can detect approximately 0.5 pg of DNA. It is well known in the art that sufficient DNA must be immobilized on the membrane to permit detection. It is desirable to have excess immobilized DNA, usually 10μg. Adding an inert polymer such as 10% (w/v) dextran sulfate (MW 500,000) or polyethylene glycol 6000 during hybridization can also increase the sensitivity of hybridization (see Ausubel *supra* at 2.10.10).

To achieve meaningful results from hybridization between a nucleotide sequence immobilized on a membrane and a labeled nucleotide sequence, a sufficient amount of the labeled nucleotide sequence must be hybridized to the immobilized nucleotide sequence following washing. Washing ensures that the labeled nucleotide sequence is hybridized only to the immobilized nucleotide sequences with a desired degree of complementarity to the labeled nucleotide sequence.

"Stringency" as used herein, refers to the temperature and ionic strength conditions, and presence or absence of certain organic solvents, during hybridization. The higher the stringency, the higher will be the degree of complementarity between the immobilized nucleotide sequences and the labeled polynucleotide sequence.

"Stringent conditions" designates those conditions under which only nucleotide sequences having a high frequency of complementary bases will hybridize.

Typical stringent conditions include, for example, (1) 0.75 M dibasic sodium phosphate/0.5 M monobasic sodium phosphate/1 mM disodium EDTA/1% sarkosyl at about 42°C for at least 30 minutes; or (2)

6.0 M urea/0.4 % sodium lauryl sulfate/0.1x SSC at about 42°C for at least 30 minutes; or (3) 0.1x SSC/0.1% SDS at about 68°C for at least 20 minutes; or (4) 1x SSC/0.1% SDS at about 55°C for about 60 minutes; or (5) 1x SSC/0.1% SDS at about 62°C for about 60 minutes; or (6) 1x SSC/0.1% SDS at about 68°C for about 60 minutes; or (7) 0.2X SSC/0.1% SDS at about 55°C for about 60 minutes; or (8) 0.2x SSC/0.1% SDS at about 62°C for about one hour; or (9) 0.2X SSC/0.1% SDS at about 68°C for about 60 minutes. For a detailed example, see CURRENT PROTOCOLS IN MOLECULAR BIOLOGY *supra* at pages 2.10.1 to 2.10.16, and Sambrook *et al.* in MOLECULAR CLONING. A LABORATORY MANUAL (Cold Spring Harbour Press, 1989) at sections 1.101 to 1.104, which are hereby incorporated by reference.

While stringent washes are typically carried out at temperatures from about 42°C to 68°C, one skilled in the art will appreciate that other temperatures may be suitable for stringent conditions. Maximum hybridization typically occurs at about 20°C to 25°C below the T_m for formation of a DNA-DNA hybrid. It is well known in the art that the T_m is the melting temperature, or temperature at which two complementary polynucleotide sequences dissociate. Methods for estimating T_m are well known in the art (see CURRENT PROTOCOLS IN MOLECULAR BIOLOGY *supra* at page 2.10.8). Maximum hybridization typically occurs at about 10°C to 15°C below the T_m for a DNA-RNA hybrid.

Other stringent conditions are well-known in the art. A skilled addressee will recognize that various factors can be manipulated to optimize the specificity of the hybridization. Optimization of the stringency of the final washes can serve to ensure a high degree of hybridization.

Methods for detecting labeled nucleotide sequences hybridized to an immobilized nucleotide sequence are well known to practitioners in the art. Such methods include autoradiography, chemiluminescent, fluorescent and colorimetric detection.

Antibodies

The invention also contemplates antibodies against the aforementioned polypeptides, fragments, variants and derivatives. Such antibodies may include any suitable antibodies which bind to or conjugate with a polypeptide, fragment, variant or derivative of the invention. For example, the antibodies may comprise polyclonal antibodies. Such antibodies may be prepared for example by injecting a polypeptide, fragment, variant or derivative of the invention into a production species, which may include mice or rabbits, to obtain polyclonal antisera. Methods of producing polyclonal antibodies are well known to those skilled in the art. Exemplary protocols which may be used are described for example in Coligan *et al.*, CURRENT PROTOCOLS IN IMMUNOLOGY, (John Wiley & Sons, Inc, 1991) which is incorporated herein by reference, and Ausubel *et al.*, (1994-1998, *supra*), in particular Section III of Chapter 11.

In lieu of the polyclonal antisera obtained in the production species, monoclonal antibodies may be produced using the standard method as for example, described in an article by Köhler and Milstein (1975, Nature **256**, 495-497) which is herein incorporated by reference, or by more recent modifications thereof as for example, described in Coligan *et al.*, (1991, *supra*) by immortalizing spleen or other antibody

producing cells derived from a production species which has been inoculated with one or more of the polypeptides, fragments, variants or derivatives of the invention.

The invention also includes within its scope antibodies which comprise Fc or Fab fragments of the polyclonal or monoclonal antibodies referred to above. Alternatively, the antibodies may comprise single chain Fv antibodies (scFvs) against the peptides of the invention. Such scFvs may be prepared, for example, in accordance with the methods described respectively in United States Patent No 5,091,513, European Patent No 239,400 or the article by Winter and Milstein (1991, Nature, **349** 293) which are incorporated herein by reference.

The antibodies of the invention may be used for affinity chromatography in isolating natural or recombinant *N. meningitidis* polypeptides. For example reference may be made to immunoaffinity chromatographic procedures described in Chapter 9.5 of Coligan *et al.*, (1995-1997, *supra*).

The antibodies can be used to screen expression libraries for variant polypeptides of the invention. The antibodies of the invention can also be used to detect *N. meningitidis* infection described hereinafter.

Detection of N. meningitidis

The presence or absence of *N. meningitidis* in a patient may determined by isolating a biological sample from a patient, mixing an antibody or antibody fragment described above with the biological sample to form a mixture, and detecting specifically bound antibody or bound fragment in the mixture which

indicates the presence of *N. meningitidis* in the sample.

The term *"biological sample"* as used herein refers to a sample which may be extracted, untreated, treated, diluted or concentrated from a patient. Suitably, the biological sample is selected from the group consisting of whole blood, serum, plasma, saliva, urine, sweat, ascitic fluid, peritoneal fluid, synovial fluid, amniotic fluid, cerebrospinal fluid, skin biopsy, and the like.

Any suitable technique for determining formation of the complex may be used. For example, an antibody or antibody fragment according to the invention having a label associated therewith may be utilized in immunoassays. Such immunoassays may include, but are not limited to, radioimmunoassays (RIAs), enzyme-linked immunosorbent assays (ELISAs) and immunochromatographic techniques (ICTs) which are well known those of skill in the art. For example, reference may be made to "CURRENT PROTOCOLS IN IMMUNOLOGY" (1994, *supra*) which discloses a variety of immunoassays that may be used in accordance with the present invention. Immunoassays may include competitive assays as understood in the art.

The label associated with the antibody or antibody fragment may include the following:

i. direct attachment of the label to the antibody or antibody fragment;

ii. indirect attachment of the label to the antibody or antibody fragment; i.e., attachment of the label to another assay reagent which subsequently binds to the antibody or antibody fragment; and

iii. attachment to a subsequent reaction product of the antibody or antibody fragment.

The label may be selected from a group including a chromogen, a catalyst, an enzyme, a fluorophore, a chemiluminescent molecule, a lanthanide ion such as Europium (Eu^{34}), a radioisotope and a direct visual label.

In the case of a direct visual label, use may be made of a colloidal metallic or non-metallic particle, a dye particle, an enzyme or a substrate, an organic polymer, a latex particle, a liposome, or other vesicle containing a signal producing substance and the like.

A large number of enzymes suitable for use as labels is disclosed in United States Patent Specifications U.S. 4,366,241, U.S. 4,843,000, and U.S. 4,849,338, all of which are herein incorporated by reference. Suitable enzyme labels useful in the present invention include alkaline phosphatase, horseradish peroxidase, luciferase, β-galactosidase, glucose oxidase, lysozyme, malate dehydrogenase and the like. The enzyme label may be used alone or in combination with a second enzyme which is in solution.

Suitably, the fluorophore is selected from a group including fluorescein isothiocyanate (FITC), tetramethylrhodamine isothiocyanate (TRITL) or R-Phycoerythrin (RPE).

The invention also extends to a method for detecting infection of patients by *N. meningitidis*, said method comprising the steps of contacting a biological sample from a patient with a polypeptide, fragment, variant or derivative of the invention, and determining the presence or absence of a complex

between said polypeptide, fragment, variant or derivative and *N. meningitidis*-specific antibodies in said serum, wherein the presence of said complex is indicative of said infection.

In a preferred embodiment, detection of the above complex is effected by detectably modifying said polypeptide, fragment, variant or derivative with a suitable label as is well known in the art and using such modified compound in a suitable immunoassay as for example described above.

In another aspect, the invention provides a method of detecting *N. meningitidis* bacteria in a biological sample suspected of containing said bacteria, said method comprising the steps of isolating the biological sample from a patient, detecting a nucleic acid sequence according to the invention in said sample which indicates the presence of said bacteria.

Detection of the said nucleic acid sequence may be determined using any suitable technique. For example, a labeled nucleic acid sequence according to the invention may be used as a probe in a Southern blot of a nucleic acid extract obtained from a patient as is well known in the art. Alternatively, a labeled nucleic acid sequence according to the invention may be utilized as a probe in a Northern blot of a RNA extract from the patient. Preferably, a nucleic acid extract from the patient is utilized in concert with oligonucleotide primers corresponding to sense and antisense sequences of a nucleic acid sequence according to the invention, or flanking sequences thereof, in a nucleic acid amplification reaction such as PCR, or the ligase chain reaction (LCR) as for example described in International Application WO89/09385 which is incorporated by reference herein.

A variety of automated solid-phase detection techniques are also appropriate. For example, very large scale immobilized primer arrays (VLSIPS™) are used for the detection of nucleic acids as for example described by Fodor *et al.*, (1991, *Science* **251**:767-777) and Kazal *et al.*, (1996, *Nature Medicine* **2**:753-759). The above generic techniques are well known to persons skilled in the art.

Pharmaceutical compositions

A further feature of the invention is the use of the polypeptide, fragment, variant or derivative of the invention ("*immunogenic agents*") as actives in a pharmaceutical composition for protecting patients against infection by *N. meningitidis*. Suitably, the pharmaceutical composition comprises a pharmaceutically-acceptable carrier.

By "*pharmaceutically-acceptable carrier*" is meant a solid or liquid filler, diluent or encapsulating substance which may be safely used in systemic administration. Depending upon the particular route of administration, a variety of pharmaceutically-acceptable carriers, well known in the art may be used. These carriers may be selected from a group including sugars, starches, cellulose and its derivatives, malt, gelatine, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water.

Any suitable route of administration may be employed for providing a patient with the composition of the invention. For example, oral, rectal, parenteral, sublingual, buccal, intravenous, intra-articular, intra-muscular, intra-dermal, subcutaneous,

inhalational, intraocular, intraperitoneal, intracerebroventricular, transdermal and the like may be employed. Intra-muscular and subcutaneous injection is appropriate, for example, for administration of immunogenic compositions, vaccines and DNA vaccines.

Dosage forms include tablets, dispersions, suspensions, injections, solutions, syrups, troches, capsules, suppositories, aerosols, transdermal patches and the like. These dosage forms may also include injecting or implanting controlled releasing devices designed specifically for this purpose or other forms of implants modified to act additionally in this fashion. Controlled release of the therapeutic agent may be effected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polylactic and polyglycolic acids and certain cellulose derivatives such as hydroxypropylmethyl cellulose. In addition, the controlled release may be effected by using other polymer matrices, liposomes and/or microspheres.

Pharmaceutical compositions of the present invention suitable for oral or parenteral administration may be presented as discrete units such as capsules, sachets or tablets each containing a pre-determined amount of one or more therapeutic agents of the invention, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association one or more immunogenic agents as described above with the carrier which constitutes one or more necessary ingredients. In general, the compositions are

prepared by uniformly and intimately admixing the immunogenic agents of the invention with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

The above compositions may be administered in a manner compatible with the dosage formulation, and in such amount as is immunogenically-effective to protect patients from *N. meningitidis* infection. The dose administered to a patient, in the context of the present invention, should be sufficient to effect a beneficial response in a patient over time such as a reduction in the level of *N. meningitidis*, or to inhibit infection by *N. meningitidis*. The quantity of the immunogenic agent(s) to be administered may depend on the subject to be treated inclusive of the age, sex, weight and general health condition thereof. In this regard, precise amounts of the immunogenic agent(s) required to be administered will depend on the judgement of the practitioner. In determining the effective amount of the immunogenic agent to be administered in the treatment or prophylaxis against *N. meningitidis*, the physician may evaluate circulating plasma levels, progression of disease, and the production of anti-*N. meningitidis* antibodies. In any event, suitable dosages of the immunogenic agents of the invention may be readily determined by those of skill in the art. Such dosages may be in the order of nanograms to milligrams of the immunogenic agents of the invention.

The above compositions may be used as therapeutic or prophylactic vaccines. Accordingly, the invention extends to the production of vaccines containing as actives one or more of the immunogenic

agents of the invention. Any suitable procedure is contemplated for producing such vaccines. Exemplary procedures include, for example, those described in NEW GENERATION VACCINES (1997, Levine *et al.*, Marcel Dekker, Inc. New York, Basel Hong Kong) which is incorporated herein by reference.

An immunogenic agent according to the invention can be mixed, conjugated or fused with other antigens, including B or T cell epitopes of other antigens. In addition, it can be conjugated to a carrier as described below.

When an haptenic peptide of the invention is used (*i.e.*, a peptide which reacts with cognate antibodies, but cannot itself elicit an immune response), it can be conjugated with an immunogenic carrier. Useful carriers are well known in the art and include for example: thyroglobulin; albumins such as human serum albumin; toxins, toxoids or any mutant crossreactive material (CRM) of the toxin from tetanus, diptheria, pertussis, *Pseudomonas*, *E. coli*, *Staphylococcus*, and *Streprococcus*; polyamino acids such as poly(lysine:glutamic acid); influenza; Rotavirus VP6, Parvovirus VP1 and VP2; hepatitis B virus core protein; hepatitis B virus recombinant vaccine and the like. Alternatively, a fragment or epitope of a carrier protein or other immnogenic protein may be used. For example, a haptenic peptide of the invention can be coupled to a T cell epitope of a bacterial toxin, toxoid or CRM. In this regard, reference may be made to U.S. Patent No 5,785,973 which is incorporated herein by reference.

In addition, a polypeptide, fragment, variant or derivative of the invention may act as a carrier

protein in vaccine compositions directed against *Neisseria*, or against other bacteria or viruses.

The immunogenic agents of the invention may be administered as multivalent subunit vaccines in combination with antigens of *N. meningitidis*, or antigens of other organisms inclusive of the pathogenic bacteria *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, *E. coli*, *S. pneumoniae* etc. Alternatively or additionally, they may be administered in concert with oligosaccharide or polysaccharide components of *N. meningitidis*.

The vaccines can also contain a physiologically-acceptable diluent or excipient such as water, phosphate buffered saline and saline.

The vaccines and immunogenic compositions may include an adjuvant as is well known in the art. Suitable adjuvants include, but are not limited to: surface active substances such as hexadecylamine, octadecylamine, octadecyl amino acid esters, lysolecithin, dimethyldioctadecylammonium bromide, N, N-dicoctadecyl-N',N'bis(2-hydroxyethyl-propanediamine), methoxyhexadecylglycerol, and pluronic polyols; polyamines such as pyran, dextransulfate, poly IC carbopol; peptides such as muramyl dipeptide and derivatives, dimethylglycine, tuftsin; oil emulsions; and mineral gels such as aluminum phosphate, aluminum hydroxide or alum; lymphokines, QuilA and immune stimulating complexes (ISCOMS).

The immunogenic agents of the invention may be expressed by attenuated viral hosts. By *"attenuated viral hosts"* is meant viral vectors which are either naturally, or have been rendered, substantially avirulent. A virus may be rendered

substantially avirulent by any suitable physical (*e.g.*, heat treatment) or chemical means (*e.g.*, formaldehyde treatment). By "*substantially avirulent*" is meant a virus whose infectivity has been destroyed. Ideally, the infectivity of the virus is destroyed without affecting the proteins which carry the immunogenicity of the virus. From the foregoing, it will be appreciated that attenuated viral hosts may comprise live viruses or inactivated viruses.

Attenuated viral hosts which may be useful in a vaccine according to the invention may comprise viral vectors inclusive of adenovirus, cytomegalovirus and preferably pox viruses such as vaccinia (see for example Paoletti and Panicali, U.S. Patent No. 4,603,112 which is incorporated herein by reference) and attenuated *Salmonella* strains (see for example Stocker, U.S. Patent No. 4,550,081 which is herein incorporated by reference). Live vaccines are particularly advantageous because they lead to a prolonged stimulus which can confer substantially long-lasting immunity.

Multivalent vaccines can be prepared from one or more microorganisms that express different epitopes of *N. meningitidis* (e.g., other surface proteins or epitopes of *N. meningitidis*). In addition, epitopes of other pathogenic microorganisms can be incorporated into the vaccine.

In a preferred embodiment, this will involve the construction of a recombinant vaccinia virus to express a nucleic acid sequence according to the invention. Upon introduction into a host, the recombinant vaccinia virus expresses the immunogenic agent, and thereby elicits a host CTL response. For example, reference may be made to U.S. Patent No

4,722,848, incorporated herein by reference, which describes vaccinia vectors and methods useful in immunization protocols.

A wide variety of other vectors useful for therapeutic administration or immunization with the immunogenic agents of the invention will be apparent to those skilled in the art from the present disclosure.

In a further embodiment, the nucleotide sequence may be used as a vaccine in the form of a "naked DNA" vaccine as is known in the art. For example, an expression vector of the invention may be introduced into a mammal, where it causes production of a polypeptide *in vivo*, against which the host mounts an immune response as for example described in Barry, M. *et al.*, (1995, *Nature*, **377**:632-635) which is hereby incorporated herein by reference.

Detection kits

The present invention also provides kits for the detection of *N. meningitidis* in a biological sample. These will contain one or more particular agents described above depending upon the nature of the test method employed. In this regard, the kits may include one or more of a polypeptide, fragment, variant, derivative, antibody, antibody fragment or nucleic acid according to the invention. The kits may also optionally include appropriate reagents for detection of labels, positive and negative controls, washing solutions, dilution buffers and the like. For example, a nucleic acid-based detection kit may include (i) a nucleic acid according to the invention (which may be used as a positive control), (ii) an oligonucleotide primer according to the invention, and

optionally a DNA polymerase, DNA ligase etc depending on the nucleic acid amplification technique employed.

Preparation of immunoreactive fragments

The invention also extends to a method of identifying an immunoreactive fragment of a polypeptide, variant or derivatives according to the invention. This method essentially comprises generating a fragment of the polypeptide, variant or derivative, administering the fragment to a mammal; and detecting an immune response in the mammal. Such response will include production of elements which specifically bind *N. meningitidis* and/or said polypeptide, variant or derivative, and/or a protective effect against *N. meningitidis* infection.

Prior to testing a particular fragment for immunoreactivity in the above method, a variety of predictive methods may be used to deduce whether a particular fragment can be used to obtain an antibody that cross-reacts with the native antigen. These predictive methods may be based on amino-terminal or carboxy-terminal sequence as for example described in Chapter 11.14 of Ausubel *et al.*, (1994-1998, *supra*). Alternatively, these predictive methods may be based on predictions of hydrophilicity as for example described by Kyte and Doolittle (1982, *J. Mol. Biol.* **157**:105-132) and Hopp and Woods (1983, *Mol. Immunol.* **20**:483-489) which are incorporated by reference herein, or predictions of secondary structure as for example described by Choo and Fasman (1978, *Ann. Rev. Biochem.* **47**:251-276) which is incorporated herein by reference.

Generally, peptide fragments consisting of 10 to 15 residues provide optimal results. Peptides as

small as 6 or as large as 20 residues have worked successfully. Such peptide fragments may then be chemically coupled to a carrier molecule such as keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA) as for example described in Sections 11.14 and 11.15 of Ausubel *et al.*, (1994-1998, *supra*).

The peptides may be used to immunize an animal as for example discussed above. Antibody titers against the native or parent polypeptide from which the peptide was selected may then be determined by, for example, radioimmunoassay or ELISA as for instance described in Sections 11.16 and 114 of Ausubel *et al.*, (1994-1998, *supra*).

Antibodies may then be purified from a suitable biological fluid of the animal by ammonium sulfate fractionation or by chromatography as is well known in the art. Exemplary protocols for antibody purification is given in Sections 10.11 and 11.13 of Ausubel *et al.*, (1994-1998, *supra*).

Immunoreactivity of the antibody against the native or parent polypeptide may be determined by any suitable procedure such as, for example, western blot.

Functional blockers

The polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 are believed to have adhesin properties. They in fact have some similarity to adhesins of *Haemophilus influenzae* which are surface antigens. Specifically they are approximately 67% homologous to the Hia protein of *H. influenzae* (Barenkamp, S. and St. Geme III, J. 1996 *Molecular Microbiology* **19**: 1215-1233), and 74% homologous to the Hsf protein of *H. influenzae* (St. Geme III, J. *et al*, 1996, *Journal of Bacteriology* **178**: 6281-6287; and U.S.

Patent No 5,646,259). For these comparisons, a gap weight of 3, and length weight of 0.01 was used using the GAP program (Deveraux, 1984, *supra*). Aligned sequences of these proteins are illustrated in FIG. 6. Thus, interruption of the function of these polypeptides would be of significant therapeutic benefit since they would prevent *N. meningitidis* bacteria from adhering to and invading cells. Interruption of the function may be effected in several ways.

For example, moieties such as chemical reagents or polypeptides which block receptors on the cell surface which interact with a polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 may be administered. These compete with the infective organism for receptor sites. Such moieties may comprise for example polypeptides of the invention, in particular fragments, or functional equivalents of these as well as mimetics.

The term *"mimetics"* is used herein to refer to chemicals which are designed to resemble particular functional regions of the proteins or peptides. Anti-idiotypic antibodies raised against the above-described antibodies which block the binding of the bacteria to a cell surface may also be used. Alternatively, moieties which interact with the receptor binding sites in the polypeptides according to SEQ ID NO 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 may effectively prevent infection of a cell by *N. meningitidis*. Such moieties may comprise blocking antibodies, peptides or other chemical reagents.

All such moieties, pharmaceutical compositions in which they are combined with pharmaceutically acceptable carriers and methods of

treating patients suffering from *N. meningitidis* infection by administration of such moieties or compositions form a further aspect of the invention.

The polypeptides of the invention may be used in the screening of compounds for their use in the above methods. For example, polypeptides of the invention may be combined with a label and exposed to a cell culture in the presence of a reagent under test. The ability of reagent to inhibit the binding of the labeled polypeptide to the cell surface can then be observed. In such a screen, the labeled polypeptides may be used directly on an organism such as *E. coli*. Alternatively, *N. meningitidis* itself may be engineered to express a modified and detectable form of the polypeptide. The use of engineered *N. meningitidis* strains in this method is preferred as it is more likely that the tertiary structure of the protein will resemble more closely that expressed in wild-type bacteria.

In order that the invention may be readily understood and put into practical effect, particular preferred embodiments will now be described by way of the following non-limiting examples.

EXAMPLE 1

Molecular cloning and subcloning and hiaNm mutant construction.

The *hiaNm* gene was initially isolated by PCR amplification using standard methods. Briefly, due to our previous work on homologues of the AIDA-I protein of *E. coli* (Jennings, M. *et al*, 1995, *Microbial Pathogenesis*, **19**: 391-407, Peak, I. *et al*, *Microbial Pathogenesis*, in press) we performed a homology

search, identifying a sequence of interest in preliminary data from the project to sequence the genome of MC58¢3 (The Institute for Genomic Research, (ftp://ftp.tigr.org/pub/data/n meningitidis/) and amplified the region of homology by PCR (polymerase chain reaction) using oligonucleotides A3A (5'-TTTGCAACGGTTCAGGCA-3', SEQ ID NO 28) and A3B (5'-TATTCAGCAGCGTATCGG-3', SEQ ID NO 29). The resulting 449 base pairs (bp) product was cloned into pT7Blue, to create plasmid pNMAIDA3. To clone the full length gene, further oligonucleotides were designed and used in an inverse PCR reaction. These oligonucleotides were A3C (SEQ ID NO 30) and A3D (SEQ ID NO 31) and correspond to the complementary sequence of A3A (SEQ ID NO 28) and A3B (SEQ ID NO 31) respectively. The template for this reaction was chromosomal DNA of MC58 which had been restriction digested with *Eag*I and then self ligated. The resulting 3kbp PCR product was cloned into the vector pCRII (Invitrogen), producing plasmid piEagA3. This was digested with *Eag*I and *EcoR*I and the resulting fragments of 1.4kbp and 1.6kbp containing cloned DNA were cloned into pBluescriptSKII, M13minus (Stratagene), resulting in piEagA3.8 and piEagA3.9. Plasmid pHiaNm was generated by PCR amplifying *hiaNm* and sequence 5'and 3' to it using oligonucleotide primers HiaNm:P (5'-TTAGATTCCACGTCCCAGATT-3', SEQ ID NO 22) and HiaNm:M (5'-CTTCCCTTCAAACCTTCC-3', SEQ ID NO 23), corresponding to nucleotide position (ntp) 113-133 and 2102-2085 respectively of SEQ ID NO 1, and cloning the product into pT7Blue. Plasmid pHiaNmΔKan was created by insertion of a kanamycin resistance cassette into the unique *Bgl*II site of pHiaNm corresponding to ntp 680 of SEQ ID No 1. The kanamycin resistance cassette

was excised from pUC4Kan (Pharmacia) with *Bam*HI. pHiaNmΔKan was transformed into *N. meningitidis* strain MC58 by incubating bacteria with plasmid DNA for 3 hours on Brain Heart Infusion agar (Acumedia Manufacturer's Inc) supplemented with 10% heated horse blood ("BHI plates") at 37°C in 5% CO_2. A single colony was picked onto fresh selective media, grown, and used for further studies. This mutant strain is designated MC58ΔHiaNm. Disruption of the *hiaNm* gene in this strain was confirmed by Southern blot using a probe corresponding to ntp 276-2054 of SEQ ID NO 1.

EXAMPLE 2

Nucleotide sequence analysis

Nucleotide sequence analysis was performed using the PRISM Dye terminator sequencing Kit with AmpliTaq DNA polymerase FS or BigDye terminator sequencing kit as suggested by the manufacturer's instructions (Perkin Elmer), in conjunction with a model 373a automated sequencer (Applied Biosystems). For each strain, *hiaNm* was amplified in three independent PCR reactions using primers HiaNm5'A2: 5'-CCAAACCCCGATTTAACC-3' (SEQ ID NO 26) and HiaNm3'A: 5'-AATCGCCACCCTTCCCTTC-3' (SEQ ID NO 27), as indicated on FIG. 1, and corresponding to ntp 230-247 and 2114-2097 of SEQ ID No 1, and the resulting products purified and pooled. This was used as template for direct sequencing on both strands. Data were analysed using the GCG programs (Deveraux *et al.* (1984) *Nucleic Acids Research* **12**, 387-395) and AssemblyLIGN (Oxford Molecular). Several oligonucleotides were generated as necessary to complete sequences. Sequences of *hiaNm* of 10 strains are shown in SEQ ID NOS 1, 3, 4,

6, 8, 10, 12, 14, 16, 18, and 20, and the deduced amino acid sequences of those genes are shown in SEQ ID NO 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Comparison of *hiaNm* from these strains indicated that they share 90-99% identity with *hiaNm* of MC58. In addition, *hiaNm* of MC58 is 62% and 68% homologous to *hia* and *hsf* of *Haemophilus influenzae* However, in the strains examined, *hiaNm* is 1770-1800 bp long. This is markedly different from the *hia* and *hsf* which are 3294 and 7059 bp long respectively. The predicted polypeptide of *hiaNm*, HiaNm, also exhibits homology to several other bacterial proteins, including AIDA-I, the adhesin involved in diffuse adherence of the diarrhoeagenic *Escherichia coli* strain 2787 (O126:H27), HMW1, another *Haemophilus* adhesin, UspA1, a high molecular weight protein of *Moraxella catarrthalis*, and SepA involved in tissue invasion of *Shigella flexneri* (Benz,I. and Schmidt,M.A., 1992, *Molecular Microbiology* **6**:1539-1546, Barenkamp,S.J. and Leininger,E.1992, *Infection and Immunity* **60**: 1302-1313, Aebi,C. *et.al* 1997,*Infection and Immunity* **65**: 4367-4377, Benjelloun-Touimi,Z *et al* 1995, *Molecular Microbiology* **17**:123-135). Homology to these (and several other proteins) occurs over the first fifty amino acids of HiaNm. Analysis of this sequence reveals the presence of a predicted signal sequence, with cleavage sites at amino acid 50 in all HiaNm sequences examined. Such long signal sequences are common to proteins located in the outer membrane of Gram-negative bacteria (Henderson, I *et al*, 1998, *Trends in Microbiology* **6**: 370-8). The proteins mentioned above to which the first fifty amino acids of HiaNm is homologous are all members of the "autotransporter" outer-membrane

protein family (Henderson, I, *supra*). This strongly suggests that HiaNm is located in the outer membrane of *N. meningitidis*.

EXAMPLE 3

Southern blot analysis

Southern blot analysis was performed using standard techniques (Sambrook *et al.*, *supra*, Ausubel *et al.*, *supra*). Briefly, genomic DNA was prepared from 70 strains of *N. meningitidis* of several serogroups, restriction digested and separated electrophoretically on an agarose gel prior to capillary transfer to a nylon membrane. These membranes were hybridized with a labeled probe. The probe used corresponded to ntp 276-2054 of SEQ ID NO 1, encompassing the entire open reading frame of *hiaNm* of strain MC58. This was labeled with DIG (dioxygenin) according to manufacturer's instructions (Boehringer Mannheim). Stringent washes were performed (two washes of 5 minutes at 22°C in 2 x SSC/0.1% SDS followed by two washes of 30 minutes, 68°C, 0.2 x SSC/0.1% SDS). Hybridization was detected colorimetrically using nitro-blue-tetrazolium/ bromo-chloryl-indolyl-phosphate (NBT/BCIP) as recommended by the manufacturer. Signals were detected in all strains examined. (FIG. 2 for example). In addition to the prototypic strain MC58, the following strains were investigated:-

TABLE 3

Strain Name	Source	Sero-group	Strain name	Source	Sero-group
PMC 3 (J1079)	2[A]	A	NGF26	1	B

PMC17 (K874)	2	A	NGG40	1	B
PMC 20 ((H79)	2	A	H15	1	B
PMC23 (K750)	2	A	SWZ107	1	B
PMC 12 (K852)	2	B	528	1	B
PMC 13 (K859)	2	B	2970	1	B
PMC 16 (K873)	2	B	1000	1	B
PMC 24 (K782)	2	B	MPJB28	3[C]	B
PMC 25 (K791)	2	B	MPJB56	3	B
PMC 27 (K816)	2	B	MPJB88	3	B
PMC 28 (K837)	2	B	MPJB157	3	B
BZ10	1[B]	B	MPJB328	3	B
BZ47	1	B	MPJB627	3	B
BZ83	1	B	MPJB820	3	B
BZ133	1	B	MPJB945	3	B
BZ147	1	B	PMC 8 (K157)	2	C
BZ163	1	B	PMC 9 (K497)	2	C
BZ169	1	B	PMC 11 (K848)	2	C
BZ198	1	B	PMC 14 (K860)	2	C
BZ232	1	B	PMC 18 (K879)	2	C
NG3/88	1	B	PMC 21 (K656)	2	C
NG4/88	1	B	PMC 29 (K841)	2	C
NG6/88	1	B	MPJC05	3	C
EG327	1	B	MPJC14	3	C
EG329	1	B	MPJC154	3	C
DK353	1	B	MPJC302	3	C
179/82	1	B	MPJC379	3	C
66/84	1	B	PMC19	2	W
DK24	1	B	MPJW025	3	W
NGH36	1	B	PMC 1 (J603)	2	X
H38	1	B	PMC 6 (K131)	2	X
H41	1	B	PMC 10 (K526)	2	Y
NGE28	1	B	PMC 22 (K685)	2	Y
NGE30	1	B	PMC 26 (K810)	2	Y
NGP20	1	B	PMC 2 ((J1049)	2	Z

[A] World Health Organization Collaborating Centre for Reference and Research on Meningococci, Oslo, Norway

[B] Public Health Laboratory Service Meningococcal Reference Laboratory, Manchester, UK

[c] Brisbane Hospitals, now in strain collection of M.P. Jennings, Department of Microbiology, University of Queensland, Brisbane, Australia.

EXAMPLE 4

Expression and partial purification of MBP-HiaNm

A plasmid vector was constructed which permitted the expression of a protein consisting of a fusion of Maltose Binding Protein and HiaNm (MBP-HiaNm). The plasmid pHiaMBP was generated by amplifying *hiaNm* from MC58 using primers Hianm-MBPA 5'-GGTCGCGGATCCATGAACAAAATATACCGCAT-3' (SEQ ID NO 24) and HiaNm-MBPB 5'-TCACCCAAGCTTAAGCCCTTACCACTGATAAC-3' (SEQ ID NO 25). These primers encompass the start and stop codons of *hiaNm* of *N. meningitidis* strain MC58 and engineered restriction sites for ease of cloning. Plasmid restriction maps and positions of oligonucleotides are shown in FIG. 1. The resultant PCR product was ligated into *Bam*HI/*Hind*III restriction digested plasmid pMALC2 (New England Biolabs), and the resultant plasmid, pHiaMBP (See FIG. 1) reintroduced to *E. coli* strain DH5α. This *E. coli* strain containing pHiaMBP was induced to express the HiaNm-MBP fusion protein under conditions recommended by the manufacturer (New England Biolabs). Cell extracts from cultures containing pHiAMBP were separated by 10% SDS-PAGE, and the fusion protein was partially purified by elution using the Mini-Gel Electro-eluter (BioRad) according to manufacturer's instructions. Fractions containing the HiaNm-MBP fusion protein were detected by Western blot using rabbit anti-MBP sera (New England Biolabs). The purity of the HiaNm-MBP

fusion protein was determined by SDS-PAGE followed by Coomassie staining, and the amount of recovered protein estimated by BCA assay (Sigma) or absorbance at a wavelength of 280nm.

EXAMPLE 5

Generation of polyclonal sera

The partially purified HiaNm-MBP fusion protein obtained in Example 4 was used to generate polyclonal sera in rabbits. Samples of eluted HiaNmMBP fusion protein were dialyzed against sterile phosphate buffered saline pH 7.4, (PBS) (Sigma). This was then mixed with adjuvant (MPL+TDM+CWS, Sigma), at a concentration of 50-150µg/mL and inoculated at two weekly intervals into two New Zealand White rabbits. Blood was taken from these rabbits. Serum was extracted by clotting at room temperature for one hour followed by overnight incubation at 4°C before centrifugation at 4000 x rpm at 4°C. The supernatant was removed and re-centrifuged. Serum was stored in aliquots at -80°C. Sera obtained were used in bactericidal assays and Western blots (see below).

To test the specificity of the sera obtained, Western blot analysis was undertaken. Briefly, proteins of *N. meningitidis* strains MC58 and MC58ΔHianm were separated electrophoretically on SDS-PAGE before electrophoretic transfer to nitrocellulose membrane using a Semi-Dry Blotter (BioRad). These were then incubated sequentially with sera and alkaline-phosphatase conjugated anti-Rabbit IgG (Sigma) before colorimetric detection with NBT/BCIP (Sigma). These experiments demonstrated that antibodies were elicited by the HiaNm-MBP fusion protein which

were specific for, and detected a band in, MC58 but not in MC58ΔHiaNm (see FIG. 4). The predicted molecular weight of the deduced polypeptide of HiaNm is 62.3 kDa. The band detected by the sera migrates at an apparent MW in excess of 150 kDa. At least three of the homologous "autotransporter" proteins reported in the literature also display such anomalous migration: the high molecular weight outer membrane proteins UspA1 and UspA2 of *Moraxella catarrhalis* have predicted molecular weights of 62.5 kDa and 88.3 kDa respectively but migrate at 85 kDa and 120 kDa, respectively and as the UspA complex at between 350 kDa and 720 kDa (Aebi, C. *et al.*, 1997, *Infection and Immunity*, 65: 4367-4377, Klingman, K.L. and Murphy, T.F., 1994, *Infection and Immunity*, 62: 1150-1155). Similarly, Hia of *Haemophilus influenzae* has a predicted molecular weight of 116 kDa but when expressed in a phage, Hia migrates at greater than 200 kDa (Barenkamp, S. and St. Geme III, J. 1996 *Molecular Microbiology* **19**: 1215-1233).

In order to confirm that HiaNm is associated with the outer membrane of *N. meningitidis*, outer membrane complexes (omc) were prepared, essentially as previously described (van der Ley, P. *et al*, 1991, *Infection and Immunity*, **59**:2963-71). Briefly, bacteria were grown overnight on Brain Heart Infusion agar (Acumedia Manufacturer's Inc) supplemented with 10% heated horse blood BHI plates, resuspended in 10 mM Tris pH 8.0 and heat killed, before sonication to disrupt the membrane. Cellular debris were removed by centrifugation at 10,000 x g (rcf, relative centrifugal force), and the supernatant recentrifuged at 50,000 x g. This pellet was resuspended in 1% sarkosyl/10 mM Tris pH8.4 and centrifuged at 10,000 x

g. The supernatant was centrifuged at 75,000 x g and the pellet resuspended in Tris pH 8.4, before quantification spectrophotometrically at a wavelength of 280nm. An aliquot of the sarkosyl-insoluble fraction, which contains outer membrane proteins, (50µl of A_{280}=3.75) was subjected to SDS-PAGE and Western blotted as described above. The results, shown in FIG. 4 demonstrate that reactivity with the anti-HiaNmMBP antisera is observed with wild type MC58, but not with MC58ΔHiaNm, in which *hiaNm* has been inactivated. The increase in reactivity with the anti-HiaMBP sera observed between whole cell samples, and the omc samples containing the same amount of total protein, in MC58 cultures is consistent with the membrane association of HiaNm.

EXAMPLE 6

Bactericidal assay

To determine whether the anti-HiaMBP antisera contained bactericidal antibodies specific for HiaNm, bactericidal assays were performed with wild type MC58 and MC58ΔHiaNm. This assay was performed by a modification of the method described by Hoogerhout *et. al.* (1995, *Infection and Immunity*, **63**: 3473-3478). Briefly, MC58 and MC58ΔHiaNm were grown overnight on BHI plates at 37°C in 5% CO_2. Bacteria from this overnight culture were subcultured under the same conditions for 4-6 hours before suspension in 1 mL PBS. Numbers of bacteria were estimated by lysis of a sample in 0.2N NaOH/1% SDS and absorbance at a wavelength of 260 nm, where A_{260}=1 = 10^9 cfu/mL. The bacterial suspension was adjusted to approximately 10^5 cfu/mL in PBS. Rabbit sera to be tested was heat

inactivated at 56°C for 45 minutes. Serum from four week old, New Zealand White rabbits was pooled and used as a source of complement (Central Animal Breeding House, University of Queensland). The assay was carried out in sterile polystyrene flat-bottomed 96 well microtitre plate. The total volume in each well was 24 µL: 12 µL of twofold serially diluted serum in PBS and 6 µL of bacterial suspension (containing between 300-900 bacteria). Sera and bacteria were incubated at room temperature for 10 minutes before addition of 6 µL of 80% complement in PBS (final concentration 20% vol/vol). Controls were a) PBS, bacteria and complement, b) PBS, bacteria and serum. After addition of all components and mixing, a 7 µL aliquot from each control well was spread on a BHI plate. The microtitre plate was then incubated at 37°C in 5% CO_2 for 60 minutes. After this incubation, a 7 µL aliquot from each well was spread on BHI plates. All BHI plates were then incubated for 14-18 hours at 37°C in 5% CO_2, and bacterial colonies counted. Serum bactericidal killing is reported as the highest reciprocal dilution at which at least 90% of bacteria were killed. Serum used was from the same rabbit and the same test bleed as used for Western blot experiments as reported in Example 5 above. These experiments consistently demonstrated reduced titers (approximately 3 fold, Table 4) of killing against MC58ΔHiaNm in comparison to the wild type strain, MC58, indicating that the anti-HiaMBP antisera contained bactericidal antibodies specific for HiaNm.

TABLE 4

STRAIN	TITRE[a]

MC58	12 (+/- 4.6)
MC58ΔHiaNm	3.5 (+/- 1)

[a] Mean of four independent experiments

DISCUSSION

Repetitive DNA has been associated with virulence determinants in some pathogenic bacteria. Southern blots using such a repetitive DNA motif revealed the presence of at least three loci which contained this motif in *N. meningitidis* strain MC58 (Peak, I. *et al.*, 1996, *FEMS Microbiology Letters*, **137**:109-114). These genes were cloned and sequence analysis of two of these repeat associated loci (*nmrep2* and *nmrep3*) revealed open reading frames of approximately 670 amino acids (Jennings, M. *et al*, 1995, *Microbial Pathogenesis*, **19**: 391-407, Peak, I. *et al*, *Microbial Pathogenesis*, in press). These exhibited homology to each other and homology to the carboxyl-terminal of the adhesin AIDA-I of *E. coli*. AIDA-I is 1286 amino acids long. The carboxyl-terminal region constitutes a putative outer membrane transport domain and the amino-terminal domain of the mature protein constitutes the adhesin domain. The amino-terminal domain crosses the membrane through the putative transport domain and is designated the passenger domain.

As Nmep2 and Nmep3 share sequence homology with the transporter domain of AIDA-I, they are thought to form membrane pores. Nmrep2 and Nmrep3 are approximately half the size of AIDA-I, and are homologous to the membrane spanning domain of AIDA-I. We hypothesized that there existed in *N. meningitidis*

a locus with homology to the amino-terminal domain of AIDA-I. We searched for such a homologue in the data from the project to sequence *N. meningitidis* strain MC58¢3 (TIGR, *supra*) and found one region with homology to a gene designated *AIDA-I* in *Haemophilus influenzae* strain Rd (HI1732) because of its homology to *AIDA-I* of *E. coli*, (Fleischmann *et. al.*, 1995 *Science* 269:496-512,). In view of the homologies noted above, the applicants decided to investigate further.

The gene was initially isolated by PCR amplification of the DNA corresponding to the 471 base pair fragment, named gnmaa84r, from *N. meningitidis* MC58 3 and the sequence was confirmed. Further PCR experiments enabled larger fragments to be amplified. These were cloned and sequence analysis undertaken as shown in FIG 1. The gene exhibited homology to the amino-terminal region of *AIDA-I* of *E. coli* and we designated it *aida3*, as it represented the third *AIDA-I* homologue in *N. meningitidis* (with *nmrep2* and *nmrep3*). Since then, the discovery of two further genes, *hia* and *hsf* from *H. influenzae* has been published (Barenkamp, S. and St. Geme III, J. 1996 *Molecular Microbiology* **19**: 1215-1233, St. Geme III, J. *et al*, 1996, *Journal of Bacteriology* **178**: 6281-6287), to which *aida3* is more similar. We have therefore re-designated this gene *hiaNm*. (HI1732, the *H. influenzae* gene first identified as an homologue of *AIDA-I* has also been re-designated *hia* in light of the reports of Barenkamp and St. Geme III).

Throughout the specification the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. It will therefore

be appreciated by those of skill in the art that, in light of the instant disclosure, various modifications and changes can be made in the particular embodiments exemplified without departing from the scope of the present invention. All such modifications and changes are intended to be included within the scope of the appendant claims

CLAIMS

1. An isolated polypeptide or fragment thereof, or variant or derivative of these, said polypeptide selected from the group consisting of:

(a) a polypeptide according to SEQ ID NO 2;
(b) a polypeptide according to SEQ ID NO 5;
(c) a polypeptide according to SEQ ID NO 7;
(d) a polypeptide according to SEQ ID NO 9;
(e) a polypeptide according to SEQ ID NO 11;
(f) a polypeptide according to SEQ ID NO 13;
(g) a polypeptide according to SEQ ID NO 15;
(h) a polypeptide according to SEQ ID NO 17;
(i) a polypeptide according to SEQ ID NO 19; and
(j) a polypeptide according to SEQ ID NO 21.

2. A polypeptide, fragment, variant or derivative according to claim 1, displaying immunological activity against one or more members selected from the group consisting of:-

(i) *N. meningitidis;*
(ii) said polypeptide;
(iii) said fragment;
(iv) said variant; and
(v) said derivative;

3. A polypeptide, fragment, variant or derivative according to claim 1, displaying immunological activity against *N. meningitidis.*

4. An isolated nucleic acid sequence encoding a polypeptide or fragment thereof, or variant or derivative of these, said polypeptide selected from the group consisting of:

(a) a polypeptide according to SEQ ID NO 2;
(b) a polypeptide according to SEQ ID NO 5;
(c) a polypeptide according to SEQ ID NO 7;
(d) a polypeptide according to SEQ ID NO 9;
(e) a polypeptide according to SEQ ID NO 11;
(f) a polypeptide according to SEQ ID NO 13;
(g) a polypeptide according to SEQ ID NO 15;
(h) a polypeptide according to SEQ ID NO 17;
(i) a polypeptide according to SEQ ID NO 19; and
(j) a polypeptide according to SEQ ID NO 21.

5. An isolated nucleic acid sequence according to claim 4, encoding a product displaying immunological activity against one or more members selected from the group consisting of:-

(i) *N. meningitidis*;
(ii) said polypeptide;
(iii) said fragment;
(iv) said variant; and
(v) said derivative.

6. An isolated nucleic acid sequence according to claim 4, encoding a product displaying immunological activity against *N. meningitidis*.

7. An isolated nucleic acid sequence selected from the group consisting of:

(1) the nucleotide sequence of SEQ ID NO 1;
(2) the nucleotide sequence of SEQ ID NO 3;
(3) the nucleotide sequence of SEQ ID NO 4;
(4) the nucleotide sequence of SEQ ID NO 6;
(5) the nucleotide sequence of SEQ ID NO 8;
(6) the nucleotide sequence of SEQ ID NO 10;
(7) the nucleotide sequence of SEQ ID NO 12;

(8) the nucleotide sequence of SEQ ID NO 14;
(9) the nucleotide sequence of SEQ ID NO 16;
(10) the nucleotide sequence of SEQ ID NO 18;
(11) the nucleotide sequence of SEQ ID NO 20;
(12) a nucleotide sequence fragment of any one of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 20; and
(13) a nucleotide sequence homologue of any of the foregoing sequences

8. A nucleic acid sequence according to claim 7, encoding a product displaying immunological activity against one or more members selected from the group consisting of:-

(i) *N. meningitidis;*
(ii) said polypeptide;
(iii) said fragment;
(iv) said variant; and
(v) said derivative.

9. A nucleic acid sequence according to claim 7, encoding a product displaying immunological activity against *N. meningitidis*.

10. The nucleic acid sequence of claim 7, wherein said homologue is obtained from the genus *Neisseria*.

11. The nucleic acid sequence of claim 5 or claim 7, wherein said homologue is obtained from a strain of *N. meningitidis*.

12. A method of obtaining a nucleotide sequence homologue comprising the steps of:-

(i) obtaining a nucleic acid extract from a suitable host;

(ii) creating primers which are optionally degenerate wherein each comprises a portion of a nucleic acid sequence according to claim 5 or claim 7; and

(iii) using said primers to amplify, via a nucleic acid amplification technique, one or more amplification products from said nucleic acid extract.

13. The method of claim 12, wherein said nucleic acid extract is obtained from the genus *Neisseria*.

14. The method of claim 12, wherein said nucleic acid extract is obtained from a strain of *N. meningitidis*.

15. The method of claim 12, wherein said primers are selected from the group consisting of SEQ ID NOS 22, 23, 24, 25, 26 ,27, 28, 29, 30, and 31.

16. The method of claim 12, wherein the nucleic acid amplification technique is PCR.

17. An expression vector comprising a nucleic acid sequence according to claim 4 or claim 7, wherein said sequence is operably linked to transcriptional and translational regulatory nucleic acid.

18. A host cell transfected or transformed with an expression vector comprising a nucleic acid sequence according to claim 4 or claim 7, wherein said sequence is operably linked to transcriptional and translational regulatory nucleic acid.

19. A method of producing a recombinant polypeptide comprising the steps of:

(A) culturing a host cell according to claim 18 such that said recombinant polypeptide is expressed from said nucleic acid; and

(B) isolating said recombinant polypeptide.

20. An antibody or antibody fragment which binds to one or more members selected from the group consisting of:-

(1) *N. meningitidis*;

(2) a polypeptide according to claim 1;

(3) a fragment of said polypeptide;

(4) a variant of said polypeptide or said fragment; and

(5) a derivative of said polypeptide or said fragment.

21. The antibody of claim 20, wherein said antibody or antibody fragment binds *N. meningitidis*.

22. A method of detecting *N. meningitidis* in a biological sample suspected of containing same, said method comprising the steps of:-

(A) isolating the biological sample from a patient;

(B) mixing the antibody or antibody fragment of claim 20 or claim 21 with the biological sample to form a mixture; and

(C) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence of *N. meningitidis*.

23. A method of detecting *N. meningitidis* bacteria in a biological sample suspected of containing said bacteria, said method comprising the steps of:-

(I) isolating the biological sample from a patient;

(II) detecting a nucleic acid sequence according to claim 4 or claim 7 in said sample which indicates the presence of said bacteria.

24. A method for diagnosing infection of patients by *N. meningitidis*, said method comprising the steps of:-

(1) contacting a biological sample from a patient with a polypeptide, fragment, variant or derivative according to claim 1; and

(2) determining the presence or absence of a complex between said polypeptide, fragment, variant or derivative and *N. meningitidis*-specific antibodies in said sample, wherein the presence of said complex is indicative of said infection.

25. Use of the polypeptide, fragment, variant or derivative according to claim 1 for the manufacture of a kit for the detection or diagnosis of *N. meningitidis* infection in humans.

26. Use of the nucleic acid sequence according to claim 4 or claim 7 for the manufacture of a kit for

the detection or diagnosis of *N. meningitidis* infection in humans.

27. Use of one or more oligonucleotide primers selected from the group consisting of SEQ ID NOS 22, 23, 24, 25, 26, 27, 28, 29, 30 and 31, and optionally a thermostable polymerase, in a kit for the detection or diagnosis of *N. meningitidis* infection in humans.

28. Use of the antibody or antibody fragment according to claim 20 or claim 21 for the manufacture of a kit for the detection or diagnosis of *N. meningitidis* infection in humans.

29. Use of a pharmaceutically effective amount of a polypeptide, fragment, variant or derivative according to claim 1 for the prevention or treatment of *N. meningitidis* infection in humans.

30. Use of a pharmaceutically effective amount of an antibody or antibody fragment according to claim 20 or claim 21 for the prevention or treatment of *N. meningitidis* infection in humans.

31. A pharmaceutical composition comprising an isolated polypeptide or fragment thereof, or a variant or derivative of these, according to claim 1.

32. The pharmaceutical of claim 31, which is a vaccine.

33. A method of preventing or treating infection of a patient by *N. meningitidis*, comprising the step

of administrating a pharmaceutically effective amount of a vaccine according to claim 32.

34. A method of identifying an immunoreactive fragment of a polypeptide, variant or derivatives according to claim 1, comprising the steps of:-

(a) generating a fragment of said polypeptide, variant or derivative;

(b) administering said fragment to a mammal; and

detecting an immune response in said mammal which response includes production of elements which specifically bind *N. meningitidis* and/or said polypeptide, variant or derivative, and/or a protective effect against *N. meningitidis* infection.

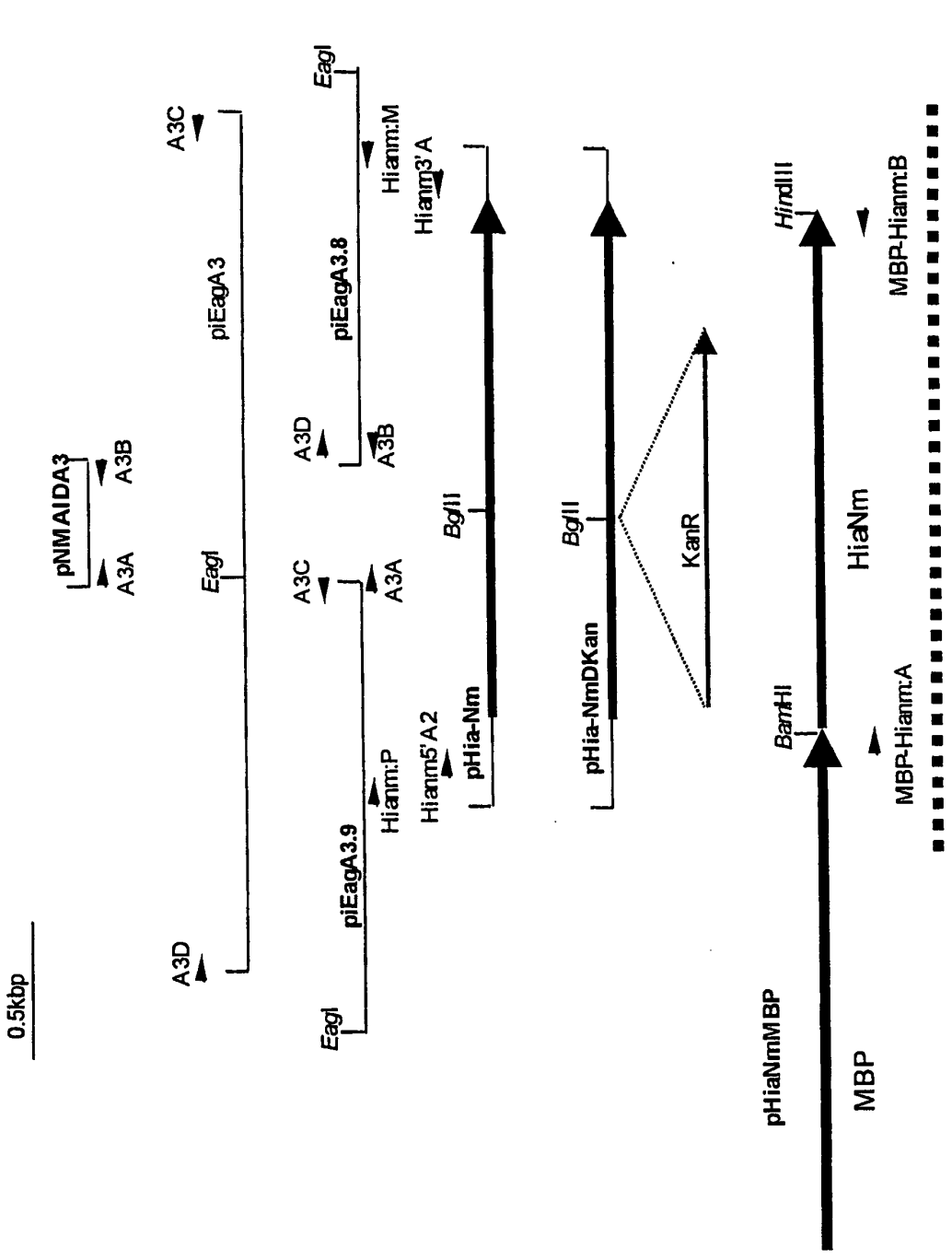
0.5kbp
pNMAIDA3
A3A
A3B
EagI
A3C
A3D
piEagA3
EagI
A3C
A3A
piEagA3.9
HiaNm:P
Hianm5'A2
BglII
pHia-Nm
A3D
A3B
piEagA3.8
EagI
Hianm:M
Hianm3'A
BglII
pHia-NmDKan
KanR
HindIII
MBP-Hianm:B
BamHI
HiaNm
MBP-Hianm:A
pHiaNmMBP
MBP

FIG. 1

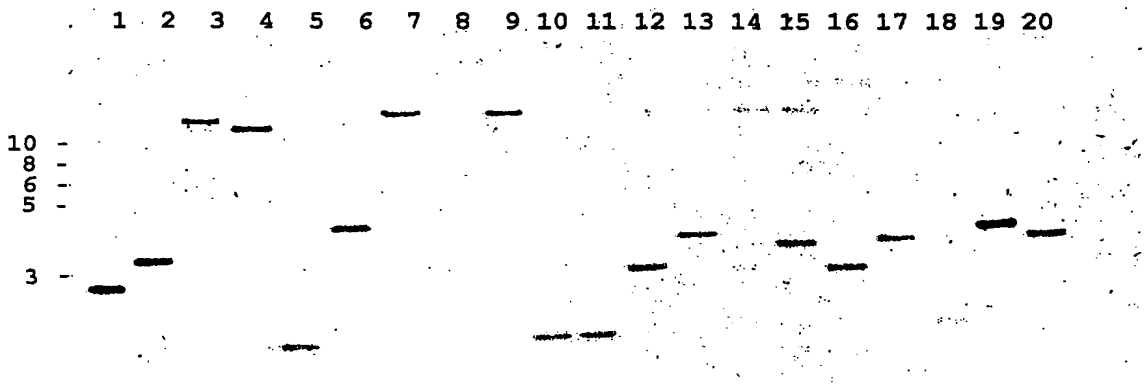

FIG. 2A

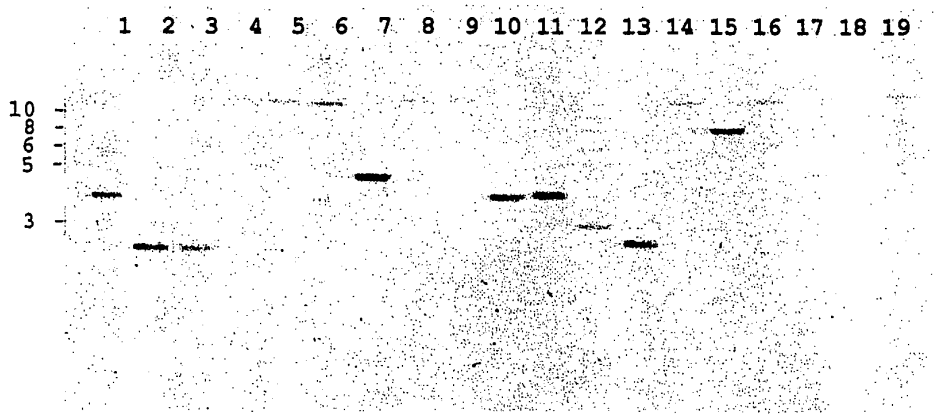

FIG. 2B

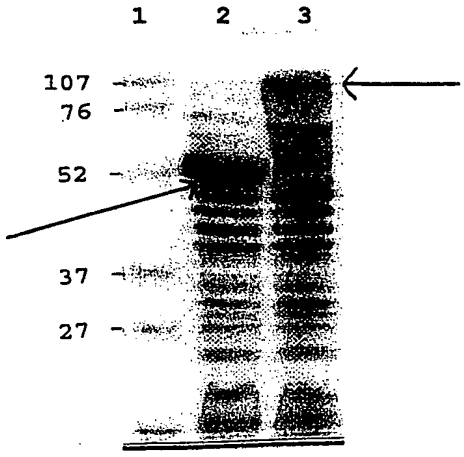

FIG. 3

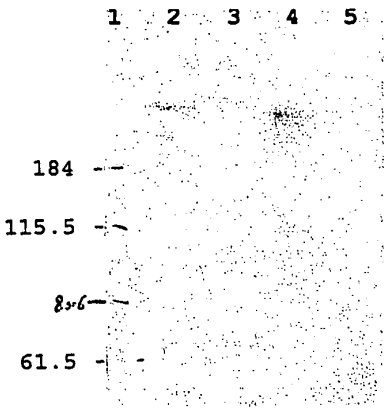

FIG. 4

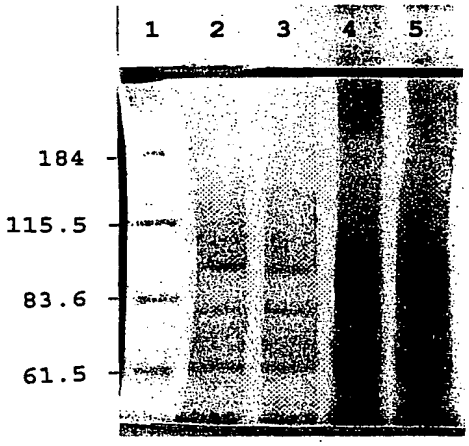

FIG. 5

FIG. 6

```
      1                                                   50
Hsf   MNKIFNVIWN VMTQTWVVVS ELTRTHTKRA SATVETAVLA TLLFATVQAN
Hia   MNKIFNVIWN VVTQTWVVVS ELTRTHTKCA SATVAVAVLA TLLSATVEAN
HiaNm MNKIYRIIWN SALNAWVVVS ELTRNHTKRA SATVKTAVLA TLLFATVQAS

      51                                                  100
Hsf   ATDEDEELDP VVRTAPVLSF HSDKEGTGEK EVTENSNWGI YFDNKGVLKA
Hia   .......... .......... .......... .......... ..........
HiaNm A......... .......... .......... .......... ..........

      101                                                 150
Hsf   GAITLKAGDN LKIKQNTDES TNASSFTYSL KKDLTDLTSV ATEKLSFGAN
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      151                                                 200
Hsf   GDKVDITSDA NGLKLAKTGN GNVHLNGLDS TLPDAVTNTG VLSSSSFTPN
Hia   .......... .......... .......... ......NNTP V.........
HiaNm .......... .......... .......... .......... ..........

      201                                                 250
Hsf   DVEKTRAATV KDVLNAGWNI KGAKTAGGNV ESVDLVSAYN NVEFITGDKN
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      251                                                 300
Hsf   TLDVVLTAKE NGKTTEVKFT PKTSVIKEKD GKLFTGKENN DTNKVTSNTA
Hia   .......... .......... .......... .......... .TNK......
HiaNm .......... .......... .......... .......... ..........

      301                                                 350
Hsf   TDNTDEGNGL VTAKAVIDAV NKAGWRVKTT TANGQNGDFA TVASGTNVTF
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      351                                                 400
Hsf   ESGDGTTASV TKDTNGNGIT VKYDAKVGDG LKFDSDKKIV ADTTALTVTG
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      401                                                 450
Hsf   GKVAEIAKED DKKKLVNAGD LVTALGNLSW KAKAEADTDG ALEGISKDQE
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      451                                                 500
Hsf   VKAGETVTFK AGKNLKVKQD GANFTYSLQD ALTGLTSITL GGTTNGGNDA
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      501                                                 550
Hsf   KTVINKDGLT ITPAGNGGTT GTNTISVTKD GIKAGNKAIT NVASGLRAYD
Hia   .......... .......... .......... .......... .....LKAYG
HiaNm .......... .......... .......... .......... ..........
```

FIG. 6 cont'd

```
      551                                                        600
Hsf   DANFDVLNNS ATDLNRHVED AYKGLLNLNE KNANKQPLVT DSTAATVGDL
Hia   DANFNFTNNS IADAEKQVQE AYKGLLNLNE KNASDKLLVE DNTAATVGNL
HiaNm ..........  ..........  ........NN ERPRKKDLYL DPVQRTVAVL

      601                                                        650
Hsf   RKLGWVVSTK NGTKEE.SNQ VKQAD.EVLF TGAGAATVTS KSENGKHTIT
Hia   RKLGWVLSSK NGTRNEKSQQ VKHAD.EVLF EGKGGVQVTS TSENGKHT..
HiaNm I....VNSDK EGT.GEKEKV EENSDWAVYF NEKGVLT...  ..........

      651                                                        700
Hsf   VSVAETKADC GLEKDGDTIK LKVDNQNTDN VLTVGNNGTA VTKGGFETVK
Hia   ..........  ..........  ..........  ..........  ..........
HiaNm ..........  ..........  ..........  ..........  ..........

      701                                                        750
Hsf   TGATDADRGK VTVKDATAND ADKKVATVKD VATAINSAAT FVKTENLTTS
Hia   ..........  ..........  ..........  ..........  ..........
HiaNm ..........  ..........  ..........  ..........  ..........

      751                                                        800
Hsf   IDEDNPTDNG KDDALKAGDT LTFKAGKNLK VKRDGKNITF DLAKNLEVKT
Hia   ..........  ..........  ..........  .......ITF ALAKDLGVKT
HiaNm ..........  .......ARE ITLKAGDNLK IKQNGTNFTY SLKKDLTDLT

      801                                                        850
Hsf   AKVSDTLTIG GNTPTGGTTA TPKVNITSTA DGLNFAKETA DASGSKNVYL
Hia   ATVSDTLTIG GGAAAGATT. TPKVNVTSTT DGLKFAKDAA GANG......
HiaNm SVGTEKLSFS ANGN...... ..KVNITSDT KGLNFAKETA GTNG......

      851                                                        900
Hsf   KGIATTLTEP SAGAKSSHVD LNVDATKKSN AASIEDVLRA GWNIQGNGNN
Hia   ..........  ..........  ..........  ..........  ..........
HiaNm ..........  ..........  ..........  ..........  ..........

      901                                                        950
Hsf   VDYVATYDTV NFTDDSTGTT TVTVTQKADG KGADVKIGAK TSVIKDHNGK
Hia   ..........  ..........  ..........  ..........  ..........
HiaNm ..........  ..........  ..........  ..........  ..........

      951                                                       1000
Hsf   LFTGKDLKDA NNGATVSEDD GKDTGTGLVT AKTVIDAVNK SGWRVTGEGA
Hia   ..........  ..........  ..........  ..........  ..........
HiaNm ..........  ..........  ..........  ..........  ..........

      1001                                                      1050
Hsf   TAETGATAVN AGNAETVTSG TSVNFKNGNA TTATVSKDNG NINVKYDVNV
Hia   ..........  ..........  ..........  ..........  ..........
HiaNm ..........  ..........  ..........  ..........  ..........

      1051                                                      1100
Hsf   GDGLKIGDDK KIVADTTTLT VTGGKVSVPA GANSVNNNKK LVNAEGLATA
Hia   ..........  ....DTT...  ..........  ..........  ..........
HiaNm ..........  ....DTT...  ..........  ..........  ..........
```

FIG. 6 cont'd

```
      1101                                                      1150
Hsf   LNNLSWTAKA DKYADGESEG ETDQEVKAGD KVTFKAGKNL KVKQSEKDFT
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      1151                                                      1200
Hsf   YSLQDTLTGL TSITLGGTAN GRNDTGTVIN KDGLTITLAN GAAAGTDASN
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      1201                                                      1250
Hsf   GNTISVTKDG ISAGNKEITN VKSALKTYKD TQNTADETQD KEFHAAVKNA
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      1251                                                      1300
Hsf   NEVEFVGKNG ATVSAKTDNN GKHTVTIDVA EAKVGDGLEK DTDGKIKLKV
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      1301                                                      1350
Hsf   DNTDGNNLLT VDATKGASVA KGEFNAVTTD ATTAQGTNAN ERGKVVVKGS
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      1351                                                      1400
Hsf   NGATATETDK KKVATVGDVA KAINDAATFV KVENDDSATI DDSPTDDGAN
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      1401                                                      1450
Hsf   DALKAGDTLT LKAGKNLKVK RDGKNITFAL ANDLSVKSAT VSDKLSLGTN
Hia   .......... .......... .......... .......... ..........
HiaNm .......... .......... .......... .......... ..........

      1451                                                      1500
Hsf   GNKVNITSDT KGLNFAKDSK TGDDANIHLN GIASTLTDTL LNSGATTNLG
Hia   .......... .......... ......VHLN GIGSTLTDTL VGSPATHIDG
HiaNm .......... .......... ......VHLN GIGSTLTDTL LNTGATTNVT

      1501                                                      1550
Hsf   GNGITDNEKK RAASVKDVLN AGWNVRGVKP ASANNQVENI DFVATYDTVD
Hia   GDQSTHY..T RAASIKDVLN AGWNIKGVKA GSTTGQSENV DFVHTYDTVE
HiaNm NDNVTDDEKK RAASVKDVLN AGWNIKGVKP GTTA..SDNV DFVRTYDTVE

      1551                                                      1600
Hsf   FVSGDKDTTS VTVESKDNGK RTEVKIGAKT SVIKDHNGKL FTGKELKDAN
Hia   FLSADTETTT VTVDSKENGK RTEVKIGAKT SVIKEKDGKL FTGKANKETN
HiaNm FLSADTKTTT VNVESKDNGK KTEVKIGVKT SVIKEKDGKL VTGKD.KGEN

      1601                                                      1650
Hsf   NNGVTVTETD GKDEGNGLVT AKAVIDAVNK AGWRVKTTGA NGQNDD...F
Hia   KVD.GANATE DADEGKGLVT AKDVIDAVNK TGWRIKTTDA NGQNGD...F
HiaNm .........GS STDEGEGLVT AKEVIDAVNK AGWRMKTTTA NGQTGQADKF
```

FIG. 6 cont'd

```
      1651                                                        1700
Hsf   ATVASGTNVT FADGNGTTAE VTKANDGSIT VKYNVKVADG LKLDGDKIVA
Hia   ATVASGTNVT FASGNGTTAT VTNGTDG.IT VKYDAKVGDG LKLDGDKIAA
HiaNm ETVTSGTNVT FASGKGTTAT VSKDDQGNIT VMYDVNVGDA LNVNQ.....

      1701                                                        1750
Hsf   DTTVLTVAD. .......GKV TAPNNGDGKK FVDASGLADA LNKLSWTATA
Hia   DTTALTVNDG KNANNPKGKV ADVASTDEKK LVTAKGLVTA LNSLSWTTTA
HiaNm .......... .......... .......... .LQNSGW... ..NLDSKAVA

      1751                                                        1800
Hsf   GKEGTGEVDP ANSAGQEVKA GDKVTFKAGD NLKIKQSGKD FTYSLKKELK
Hia   AEADGGTLD. GNASEQEVKA GDKVTFKAGK NLKVKQEGAN FTYSLQDALT
HiaNm G..SSGKVIS GNVSPSKGKM DETVNINAGN NIEITRNGKN I..DIATSMT

      1801                                                        1850
Hsf   .DLTSVEFKD ANGGTGSEST KITKDGLTIT PANGAGAAGA NTANTISVTK
Hia   .GLTSITLGT GNNGA...KT EINKDGLTIT PANG...AGA NNANTISVTK
HiaNm PQFSSVSLG. .......... .......... .......AGA D.APTLSV..

      1851                                                        1900
Hsf   DGISAGNKAV TNVVSGLKKF GDGHTLANGT VAD.FEKHYD NAYKDLTNLD
Hia   DGISAGGQSV KNVVSGLKKF GDANFDPLTS SADNLTKQND DAYKGLTNLD
HiaNm .......... .......... .......... .......... ..........

      1901                                                        1950
Hsf   EKGADNN.PT VADNTAATVG DLRGLGWVIS ADKTTGEPNQ EYNAQVRNAN
Hia   EKGTDKQTPV VADNTAATVG DLRGLGWVIS ADKTTGGST. EYHDQVRNAN
HiaNm .......... .......... .......... .......... ..........

      1951                                                        2000
Hsf   EVKFKSGNGI NVSGKTLNGT RVITFELAKG EVVKSNEFTV KNADGSETNL
Hia   EVKFKSGNGI NVSGKTVNGR REITFELAKG EVVKSNEFTV KETNGKETSL
HiaNm .....DGDAL NVGSK..... .......... .......... ..........

      2001                                                        2050
Hsf   VKVGDMYYSK EDIDPATSKP ..MTGKT..E KYKVENGKVV SANGSKTEVT
Hia   VKVGDKYYSK EDIDLTTGQP KLKDGNTVAA KYQDKGGKVV SVTD.NTEAT
HiaNm .......... .......... .......... ....KDNKPV R.........

      2051                                                        2100
Hsf   LTNKGSGYVT GNQVADAIAK SGFELGLADA AEAEKAFAES AKDKQLSKDK
Hia   ITNKGSGYVT GNQVADAIAK SGFELGLADE ADAKRAFDD. .KTKALSAGT
HiaNm ITNVAPG... .......... .......... .......... ..........

      2101                                                        2150
Hsf   AETVNAHDKV RFANGLNTKV SAATVESTDA NGDKVTTTFV KTDVELPLTQ
Hia   TEIVNAHDKV RFANGLNTKV SAATVESTDA NGDKVTTTFV KTDVELPLTQ
HiaNm .......... .......... .......... .......... ..........

      2151                                                        2200
Hsf   IYNTDANGNK I...VKKADG KWYELNADGT AS.NKEVTLG NVDANGKKVV
Hia   IYNTDANGKK ITKVVKDGQT KWYELNADGT ADMTKEVTLG NVDSDGKKVV
HiaNm .......... ....VKEGD. .......... .......... ..........
```

FIG. 6 cont'd

```
      2201                                                2250
  Hsf KVTENGADKW YYTNADGAAD KTKGEVSNDK VSTDEKHVVR LDPNNQSNGK
  Hia K...DNDGKW YHAKADGTAD KTKGEVSNDK VSTDEKHVVS LDPNDQSKGK
HiaNm .......... .......... .......... .......... ..........

      2251                                                2300
  Hsf GVVIDNVANG EISATSTDAI NGSQLYAVAK GVTNLAGQVN NLEGKVNKVG
  Hia GVVIDNVANG DISATSTDAI NGSQLYAVAK GVTNLAGQVN NLEGKVNKVG
HiaNm ...VTNVA.. .......... ...QLKGVA. .........Q NLNNRIDNVD

      2301                                                2350
  Hsf KRADAGTASA LAASQLPQAT MPGKSMVAIA GSSYQGQNGL AIGVSRISDN
  Hia KRADAGTASA LAASQLPQAT MPGKSMVAIA GSSYQGQNGL AIGVSRISDN
HiaNm GNARAGIAQA IATAGLVQAY LPGKSMMAIG GGTYRGEAGY AIGYSSISDG

      2351                  2378
  Hsf GKVIIRLSGT TNSQGKTGVA AGVGYQW*
  Hia GKVIIRLSGT TNSQGKTGVA AGVGYQW*
HiaNm GNWIIKGTAS GNSRGHFGAS ASVGYQW*
```

FIG. 7

```
          1                                                  50
eg329     MNEILRIIWN SALNAWVVVS ELTRNHTKRA SATVKTAVLA TLLFATVQAS
pmc21     MNKIYRIIWN SALNAWVVVS ELTRNHTKRA SATVKTAVLA TLLFATVQAS
HiaNm     MNKIYRIIWN SALNAWVVVS ELTRNHTKRA SATVKTAVLA TLLFATVQAS
  h15     MNKIYRIIWN SALNAWVVVS ELTRNHTKRA SATVATAVLA TLLFATVQAN
 BZ10     MNKISRIIWN SALNAWVVVS ELTRNHTKRA SATVATAVLA TLLFATVQAN
bz198     MNKIYRIIWN SALNAWVVVS ELTRNHTKRA SATVATAVLA TLLFATVQAN
eg327     MNKIYRIIWN SALNAWVAVS ELTRNHTKRA SATVATAVLA TLLFATVQAS
  h38     MNKIYRIIWN SALNAWVAVS ELTRNHTKRA SATVKTAVLA TLLFATVQAN
  h41     MNKIYRIIWN SALNAWVAVS ELTRNHTKRA SATVKTAVLA TLLFATVQAN
  p20     MNKIYRIIWN SALNAWVVVS ELTRNHTKRA SATVATAVLA TLLSATVQAN

          51                                                 100
eg329     ANNE.EQEED LYLDPVLRTV AVLIVNSDKE GTGEKEKVEE NSDWAVYFNE
pmc21     ANNE.EQEED LYLDPVQRTV AVLIVNSDKE GTGEKEKVEE NSDWAVYFNE
HiaNm     ANNERPRKKD LYLDPVQRTV AVLIVNSDKE GTGEKEKVEE NSDWAVYFNE
  h15     ATD....DDD LYLEPVQRTA VVLSFRSDKE GTGEKE.GTE DSNWAVYFDE
 BZ10     ATD....DDD LYLEPVQRTA VVLSFRSDKE GTGEKE.GTE DSNWAVYFDE
bz198     ATD....DDD LYLEPVQRTA VVLSFRSDFE GTGEKE.GTE DSNWAVYFDE
eg327     TTD....DDD LYLEPVQRTA VVLSFRSDKE GTGEKE.VTE DSNWGVYFDK
  h38     ATDE...DEE EELEPVVRSA LVLQFMIDKE GNGENE.STG NIGWSIYYDN
  h41     ATDE...DEE EELESVQRS. VVGSIQASME GSVELETI.. ..SLSMTNDS
  p20     ATDT...DED EELESVARSA LVLQFMIDKE GNGEIE.STG DIGWSIYYDD

          101                                                150
eg329     KGVLTA.REI TLKAGDNLKI KQ........ ..NGTNFTYS LKKDLTDLTS
pmc21     KGVLTA.REI TLKAGDNLKI KQ........ ..NGTNFTYS LKKDLTDLTS
HiaNm     KGVLTA.REI TLKAGDNLKI KQ........ ..NGTNFTYS LKKDLTDLTS
  h15     KRVLKA.GAI TLKAGDNLKI KQNTNENTNE NTNDSSFTYS LKKDLTDLTS
 BZ10     KRVLKA.GAI TLKAGDNLKI KQNTNENTNE NTNDSSFTYS LKKDLTDLTS
bz198     KRVLKA.GAI TLKAGDNLKI KQ....NTNE NTNDSSFTYS LKKDLTDLTS
eg327     KGVLTA.GTI TLKAGDNLKI KQ....NTNE NTNASSFTYS LKKDLTDLTS
  h38     HNTLHG.ATV TLKAGDNLKI KQNTNKNTNE NTNDSSFTYS LKKDLTDLTS
  h41     KEFVDPYIVV TLKAGDNLKI KQ....NTNE NTNASSFTYS LKKDLTGLIN
  p20     HNTLHG.ATV TLKAGDNLKI KQ........ ..SGKDFTYS LKKELKDLTS

          151                                                200
eg329     VGTEKLSFSA NGNKVNITSD TKGLNFAKET AGTNGDTTVH LNGIGSTLTD
pmc21     VGTEKLSFSA NGNKVNITSD TKGLNFAKET AGTNGDTTVH LNGIGSTLTD
HiaNm     VGTEKLSFSA NGNKVNITSD TKGLNFAKET AGTNGDTTVH LNGIGSTLTD
  h15     VETEKLSFGA NGNKVNITSD TKGLNFAKET AGTNGDPTVH LNGIGSTLTD
 BZ10     VETEKLSFGA NGNKVNITSD TKGLNFAKET AGTNGDPTVH LNGIGSTLTD
bz198     VETEKLSFGA NGNKVNITSD TKGLNFAKET AGTNGDPTVH LNGIGSTLTD
eg327     VGTEKLSFSA NSNKVNITSD TKGLNFAKKT AETNGDTTVH LNGIGSTLTD
  h38     VETEKLSFGA NGNKVNITSD TKGLNFAKET AGTNGDTTVH LNGIGSTLTD
  h41     VETEKLSFGA NGKKVNIISD TKGLNFAKET AGTNGDTTVH LNGIGSTLTD
  p20     VETEKLSFGA NGNKVNITSD TKGLNFAKET AGTNGDPTVH LNGIGSTLTD
```

FIG. 7 cont'd

```
      201                                                        250
eg329 TLLNTGATTN VTNDNVTDDE KKRAASVKDV LNAGWNIKGV KPGTTA..SD
pmc21 TLLNTGATTN VTNDNVTDDE KKRAASVKDV LNAGWNIKGV KPGTTA..SD
HiaNm TLLNTGATTN VTNDNVTDDE KKRAASVKDV LNAGWNIKGV KPGTTA..SD
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bz198 TLLNTGATTN VTNDNVTDDE KKRAASVKDV LNAGWNIKGV KPGTTA..SD
eg327 TLLNTGATTN VTNDNVTDDE KKRAASVKDV LNAGWNIKGV KPGTTA..SD
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  h41 MLLNTGATTN VTNDNVTDDE KKRAASVKDV LNAGWNIKGV KPGTTA..SD
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      351                                                        400
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FIG. 7 cont'd

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HiaNm     NSGWNLDSKA VAGSSGKVIS GNVSPSKGKM DETVNINAGN NIEITRNGKN
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 BZ10     NSGWNLDSKA VAGSSGKVIS GNVSPSKGKM DETVNINAGN NIEITRNGKN
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eg327     NSGWNLDSKA VAGSSGKVIS GNVSPSKGKM DETVNINAGN NIEITRNGKN
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  h41     NSGWNLDSKA VAGSSGKVIS GNVSPSKGKM DETVNINAGN NIEITRNGKN
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pmc21     IDIATSMTPQ FSSVSLGAGA DAPTLSVDGD .ALNVGSKKD NKPVRITNVA
HiaNm     IDIATSMTPQ FSSVSLGAGA DAPTLSVDGD .ALNVGSKKD NKPVRITNVA
  h15     IDIATSMTPQ FSSVSLGAGA DAPTLSVDDE GALNVGSKDA NKPVRITNVA
 BZ10     IDIATSMTPQ FSSVSLGAGA DAPTLSVDDE GALNVGSKDA NKPVRITNVA
bz198     IDIATSMAPQ FSSVSLGAGA DAPTLSVDDE GALNVGSKDT NKPVRITNVA
eg327     IDIATSMTPQ FSSVSLGAGA DAPTLSVDDE GALNVGSKDA NKPVRITNVA
  h38     IDIATSMTPQ FSSVSLGAGA DAPTLSVDDK GALNVGSKDA NKPVRITNVA
  h41     IDIATSMTPQ FSSVSLGAGA DAPTLSVDDE GALNVGSKDA NKPVRITNVA
  p20     IDIATSMTPQ FSSVSLGAGA DAPTLSVDDE GALNVGSKDA NKPVRITNVA

          501                                                       550
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pmc21     PGVKEGDVTN VAQLKGVAQN LNNRIDNVDG NARAGIAQAI ATAGLVQAYL
HiaNm     PGVKEGDVTN VAQLKGVAQN LNNRIDNVDG NARAGIAQAI ATAGLVQAYL
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eg327     PGVKEGDVTN VAQLKGVAQN LNNHIDNVDG NARAGIAQAI ATAGLVQAYL
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  h41     PGVKEGDVTN VAQLKGVAQN LNNRIDNVNG NARAGIAQAI ATAGLVQAYL
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          551                                                       600
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pmc21     PGKSMMAIGG GTYRGEAGYA IGYSSISDGG NWIIKGTASG NSRGHFGASA
HiaNm     PGKSMMAIGG GTYRGEAGYA IGYSSISDGG NWIIKGTASG NSRGHFGASA
  h15     PGKSMMAIGG GTYRGEAGYA IGYSSISDTG NWVIKGTASG NSRGHFGASA
 BZ10     PGKSMMAIGG GTYRGEAGYA IGYSSISDTG NWVIKGTASG NSRGHFGTSA
bz198     PGKSMMAIGG DTYRGEAGYA IGYSSISDGG NWIIKGTASG NSRGHFGASA
eg327     PGKSMMAIGG GTYRGEAGYA IGYSSISDGG NWIIKGTASG NSRGHFGASA
  h38     PGKSMMAIGG GTYRGEAGYA IGYSSISDGG NWIIKGTASG NSRGHFGASA
  h41     PGKSMMAIGG GTYLGEAGYA IGYSSISAGG NWIIKGTASG NSRGHFGASA
  p20     PGKSMMAIGG GTYLGEAGYA IGYSSISDTG NWVIKGTASG NSRGHFGTSA
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FIG. 7 cont'd

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pmc21   SVGYQW*
HiaNm   SVGYQW*
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SEQUENCE LISTING

<110> Peak, Ian R. (U.S. only)
Jennings, Michael P. (U.S. only)
Moxom, Edward R. (U.S. only)
University of Queensland (except U.S.)
Isis Innovations Limited (except U.S.)

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Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp Val Val Val Ser Glu Leu
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Thr Arg Asn His Thr Lys Arg Ala Ser Ala Thr Val Lys Thr Ala Val
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Leu Ala Thr Leu Leu Phe Ala Thr Val Gln Ala Ser Ala Asn Asn Glu
40 45 50

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Arg Pro Arg Lys Lys Asp Leu Tyr Leu Asp Pro Val Gln Arg Thr Val
55 60 65 70

gcc gtg ttg ata gtc aat tcc gat aaa gaa ggc acg gga gaa aaa gaa 533
Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly Thr Gly Glu Lys Glu
75 80 85

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Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr Phe Asn Glu Lys Gly
             90                  95                  100

gta cta aca gcc aga gaa atc acc ctc aaa gcc ggc gac aac ctg aaa   629
Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala Gly Asp Asn Leu Lys
        105                 110                 115

atc aaa caa aac ggc aca aac ttc acc tac tcg ctg aaa aaa gac ctc   677
Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser Leu Lys Lys Asp Leu
    120                 125                 130

aca gat ctg acc agt gtt gga act gaa aaa tta tcg ttt agc gca aac   725
Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu Ser Phe Ser Ala Asn
135                 140                 145                 150

ggc aat aaa gtc aac atc aca agc gac acc aaa ggc ttg aat ttt gcg   773
Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala
                155                 160                 165

aaa gaa acg gct ggg acg aac ggc gac acc acg gtt cat ctg aac ggt   821
Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr Val His Leu Asn Gly
            170                 175                 180

att ggt tcg act ttg acc gat acg ctg ctg aat acc gga gcg acc aca   869
Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr
        185                 190                 195

aac gta acc aac gac aac gtt acc gat gac gag aaa aaa cgt gcg gca   917
Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala
    200                 205                 210

agc gtt aaa gac gta tta aac gct ggc tgg aac att aaa ggc gtt aaa   965
Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys
215                 220                 225                 230

ccc ggt aca aca gct tcc gat aac gtt gat ttc gtc cgc act tac gac   1013
Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp
                235                 240                 245

aca gtc gag ttc ttg agc gca gat acg aaa aca acg act gtt aat gtg   1061
Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val
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gaa agc aaa gac aac ggc aag aaa acc gaa gtt aaa atc ggt gtg aag   1109
Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val Lys Ile Gly Val Lys
        265                 270                 275

act tct gtt att aaa gaa aaa gac ggt aag ttg gtt act ggt aaa gac   1157
Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Asp
    280                 285                 290

aaa ggc gag aat ggt tct tct aca gac gaa ggc gaa ggc tta gtg act   1205
Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr
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aca aca acc gct aat ggt caa aca ggt caa gct gac aag ttt gaa acc   1301
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gcg act gta agt aaa gat gat caa ggc aac atc act gtt atg tat gat   1397
Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile Thr Val Met Tyr Asp
    360                 365                 370

gta aat gtc ggc gat gcc cta aac gtc aat cag ctg caa aac agc ggt   1445
Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly
375                 380                 385                 390

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Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile
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agc ggc aat gtt tcg ccg agc aag gga aag atg gat gaa acc gtc aac   1541
Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn
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att aat gcc ggc aac aac atc gag att acc cgc aac ggt aaa aat atc   1589
Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile
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gac atc gcc act tcg atg acc ccg cag ttt tcc agc gtt tcg ctc ggc   1637
Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly
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gcg ggg gcg gat gcg ccc act ttg agc gtg gat ggg gac gca ttg aat   1685
Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp Gly Asp Ala Leu Asn
455                 460                 465                 470

gtc ggc agc aag aag gac aac aaa ccc gtc cgc att acc aat gtc gcc   1733
Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg Ile Thr Asn Val Ala
                475                 480                 485

ccg ggc gtt aaa gag ggg gat gtt aca aac gtc gca caa ctt aaa ggc   1781
Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly
            490                 495                 500

gtg gcg caa aac ttg aac aac cgc atc gac aat gtg gac ggc aac gcg   1829
Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala
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cgt gcg ggc atc gcc caa gcg att gca acc gca ggt ctg gtt cag gcg   1877
Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu Val Gln Ala
    520                 525                 530

tat ttg ccc ggc aag agt atg atg gcg atc ggc ggc ggc act tat cgc   1925
Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg
535                 540                 545                 550

ggc gaa gcc ggt tac gcc atc ggc tac tcc agt att tcc gac ggc gga   1973
Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Gly Gly
                555                 560                 565

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ggt gct tcc gca tct gtc ggt tat cag tgg taa gggctttatc gcctgtctgc 2074
Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
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Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
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Ala Ser Ala Asn Asn Glu Arg Pro Arg Lys Lys Asp Leu Tyr Leu Asp
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Pro Val Gln Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu
 65                  70                  75                  80

Gly Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val
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Tyr Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys
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Ala Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr
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Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys
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Leu Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr
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Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr
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Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu
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Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp
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Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys
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Met Asn Lys Ile Ser Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
            20                  25                  30

acc gtg gcg acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag   144
Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
        35                  40                  45

gcg aat gct acc gat gac gac gat tta tat tta gaa ccc gta caa cgc   192
Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
    50                  55                  60

act gct gtc gtg ttg agc ttc cgt tcc gat aaa gaa ggc acg gga gaa   240
Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
65                  70                  75                  80

aaa gaa ggt aca gaa gat tca aat tgg gca gta tat ttc gac gag aaa   288
Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
                85                  90                  95

aga gta cta aaa gcc gga gca atc acc ctc aaa gcc ggc gac aac ctg   336
Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

aaa atc aaa caa aac acc aat gaa aac acc aat gaa aac acc aat gac   384
Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Glu Asn Thr Asn Asp
        115                 120                 125

agt agc ttc acc tac tcc ctg aaa aaa gac ctc aca gat ctg acc agt   432
Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser
    130                 135                 140

gtt gaa act gaa aaa tta tcg ttt ggc gca aac ggt aat aaa gtc aac   480
Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn
145                 150                 155                 160

atc aca agc gac acc aaa ggc ttg aat ttt gcg aaa gaa acg gct ggg   528
Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
                165                 170                 175

acg aac ggc gac ccc acg gtt cat ctg aac ggt atc ggt tcg act ttg   576
Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
            180                 185                 190

acc gat acg ctg ctg aat acc gga gcg acc aca aac gta acc aac gac   624
Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
        195                 200                 205

aac gtt acc gat gac gag aaa aaa cgt gcg gca agc gtt aaa gac gta   672
Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
    210                 215                 220

tta aac gca ggc tgg aac att aaa ggc gtt aaa ccc ggt aca aca gct   720
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Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala
225                 230                 235                 240

tcc gat aac gtc gat ttc gtc cgc act tac gac aca gtc gag ttc ttg   768
Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu
                245                 250                 255

agc gca gat acg aaa aca acg act gtt aat gtg gaa agc aaa gac aac   816
Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn
            260                 265                 270

ggc aag aga acc gaa gtt aaa atc ggt gcg aag act tct gtt att aaa   864
Gly Lys Arg Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys
        275                 280                 285

gaa aaa gac ggt aag ttg gtt act ggt aaa ggc aaa ggc gag aat ggt   912
Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Gly Glu Asn Gly
    290                 295                 300

tct tct aca gac gaa ggc gaa ggc tta gtg act gca aaa gaa gtg att   960
Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile
305                 310                 315                 320

gat gca gta aac aag gct ggt tgg aga atg aaa aca aca acc gct aat  1008
Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn
                325                 330                 335

ggt caa aca ggt caa gct gac aag ttt gaa acc gtt aca tca ggc aca  1056
Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr
            340                 345                 350

aaa gta acc ttt gct agt ggt aat ggt aca act gcg act gta agt aaa  1104
Lys Val Thr Phe Ala Ser Gly Asn Gly Thr Thr Ala Thr Val Ser Lys
        355                 360                 365

gat gat caa ggc aac atc act gtt aag tat gat gta aat gtc ggc gat  1152
Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp
    370                 375                 380

gcc cta aac gtc aat cag ctg caa aac agc ggt tgg aat ttg gat tcc  1200
Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser
385                 390                 395                 400

aaa gcg gtt gca ggt tct tcg ggc aaa gtc atc agc ggc aat gtt tcg  1248
Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser
                405                 410                 415

ccg agc aag gga aag atg gat gaa acc gtc aac att aat gcc ggc aac  1296
Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn
            420                 425                 430

aac atc gag att acc cgc aac ggc aaa aat atc gac atc gcc act tcg  1344
Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser
        435                 440                 445

atg acc ccg caa ttt tcc agc gtt tcg ctc ggc gcg ggg gcg gat gcg  1392
Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala
    450                 455                 460

ccc act tta agc gtg gat gac gag ggc gcg ttg aat gtc ggc agc aag  1440
Pro Thr Leu Ser Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys
465                 470                 475                 480

gat gcc aac aaa ccc gtc cgc att acc aat gtc gcc ccg ggc gtt aaa  1488
Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys
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                485                 490                 495

gag ggg gat gtt aca aac gtc gca caa ctt aaa ggt gtg gcg caa aac   1536
Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn
            500                 505                 510

ttg aac aac cgc atc gac aat gtg gac ggc aac gcg cgc gcg ggt atc   1584
Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile
        515                 520                 525

gcc caa gcg att gca acc gca ggt ttg gct cag gcc tat ttg ccc ggc   1632
Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly
    530                 535                 540

aag agt atg atg gcg atc ggc ggc ggt act tat cgc ggc gaa gcc ggt   1680
Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly
545                 550                 555                 560

tac gcc atc ggc tac tcg agc att tct gac act ggg aat tgg gtt atc   1728
Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile
                565                 570                 575

aag ggc acg gct tcc ggc aat tcg cgc ggt cat ttc ggt act tcc gca   1776
Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Thr Ser Ala
            580                 585                 590

tct gtc ggt tat cag tgg taa                                      1797
Ser Val Gly Tyr Gln Trp
        595


<210> 5
<211> 598
<212> PRT
<213> Neisseria meningitidis

<400> 5
Met Asn Lys Ile Ser Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
     50                  55                  60

Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65                  70                  75                  80

Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
                 85                  90                  95

Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Glu Asn Thr Asn Asp
        115                 120                 125

Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser
    130                 135                 140

Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn
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145                 150                 155                 160

Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
                165                 170                 175

Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
            180                 185                 190

Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
        195                 200                 205

Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
    210                 215                 220

Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala
225                 230                 235                 240

Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu
                245                 250                 255

Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn
            260                 265                 270

Gly Lys Arg Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys
        275                 280                 285

Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Gly Glu Asn Gly
    290                 295                 300

Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile
305                 310                 315                 320

Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn
                325                 330                 335

Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr
            340                 345                 350

Lys Val Thr Phe Ala Ser Gly Asn Gly Thr Thr Ala Thr Val Ser Lys
        355                 360                 365

Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp
    370                 375                 380

Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser
385                 390                 395                 400

Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser
                405                 410                 415

Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn
            420                 425                 430

Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser
        435                 440                 445

Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala
    450                 455                 460

Pro Thr Leu Ser Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys
465                 470                 475                 480

Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys
                485                 490                 495
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xi

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Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn
            500                 505                 510

Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile
        515                 520                 525

Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly
    530                 535                 540

Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly
545                 550                 555                 560

Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile
                565                 570                 575

Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Thr Ser Ala
            580                 585                 590

Ser Val Gly Tyr Gln Trp
        595


<210> 6
<211> 1785
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1785)

<400> 6
atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg   48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

acc gtg gcg acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag   144
Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

gcg aat gct acc gat gac gac gat tta tat tta gaa ccc gta caa cgc   192
Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
     50                  55                  60

act gct gtc gtg ttg agc ttc cgt tcc gat aaa gaa ggc acg gga gaa   240
Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65                  70                  75                  80

aaa gaa ggt aca gaa gat tca aat tgg gca gta tat ttc gac gag aaa   288
Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
                 85                  90                  95

aga gta cta aaa gcc gga gca atc acc ctc aaa gcc ggc gac aac ctg   336
Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

aaa atc aaa caa aac acc aat gaa aac acc aat gac agt agc ttc acc   384
Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Asp Ser Ser Phe Thr
        115                 120                 125

tac tcc ctg aaa aaa gac ctc aca gat ctg acc agt gtt gaa act gaa   432
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Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Glu Thr Glu
    130                 135                 140

aaa tta tcg ttt ggc gca aac ggt aat aaa gtc aac atc aca agc gac   480
Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp
145                 150                 155                 160

acc aaa ggc ttg aat ttt gcg aaa gaa acg gct ggg acg aac ggc gac   528
Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp
                165                 170                 175

ccc acg gtt cat ctg aac ggt atc ggt tcg act ttg acc gat acg ctg   576
Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu
            180                 185                 190

ctg aat acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat   624
Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp
        195                 200                 205

gac gag aaa aaa cgt gcg gca agc gtt aaa gac gta tta aac gca ggc   672
Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly
    210                 215                 220

tgg aac att aaa ggc gtt aaa ccc ggt aca aca gct tcc gat aac gtt   720
Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val
225                 230                 235                 240

gat ttc gtc cgc act tac gac aca gtc gag ttc ttg agc gca gat acg   768
Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr
                245                 250                 255

aaa aca acg act gtt aat gtg gaa agc aaa gac aac ggc aag aaa acc   816
Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr
            260                 265                 270

gaa gtt aaa atc ggt gcg aag act tct gtt att aaa gaa aaa gac ggt   864
Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly
        275                 280                 285

aag ttg gtt act ggt aaa ggc aaa gac gag aat ggt tct tct aca gac   912
Lys Leu Val Thr Gly Lys Gly Lys Asp Glu Asn Gly Ser Ser Thr Asp
    290                 295                 300

gaa ggc gaa ggc tta gtg act gca aaa gaa gtg att gat gca gta aac   960
Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn
305                 310                 315                 320

aag gct ggt tgg aga atg aaa aca aca acc gct aat ggt caa aca ggt  1008
Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly
                325                 330                 335

caa gct gac aag ttt gaa acc gtt aca tca ggc aca aat gta acc ttt  1056
Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe
            340                 345                 350

gct agt ggt aaa ggt aca act gcg act gta agt aaa gat gat caa ggc  1104
Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly
        355                 360                 365

aac atc act gtt aag tat gat gta aat gtc ggc gat gcc cta aac gtc  1152
Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val
    370                 375                 380

aat cag ctg caa aac agc ggt tgg aat ttg gat tcc aaa gcg gtt gca  1200
Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala
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385                 390                 395                 400

ggt tct tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga   1248
Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly
                405                 410                 415

aag atg gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att   1296
Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile
            420                 425                 430

acc cgc aac ggt aaa aat atc gac atc gcc act tcg atg gcg ccg cag   1344
Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Ala Pro Gln
        435                 440                 445

ttt tcc agc gtt tcg ctc ggt gcg ggg gcg gat gcg ccc act ttg agc   1392
Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser
    450                 455                 460

gtg gat gac gag ggc gcg ttg aat gtc ggc agc aag gat acc aac aaa   1440
Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Thr Asn Lys
465                 470                 475                 480

ccc gtc cgc att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt   1488
Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val
                485                 490                 495

aca aac gtc gca caa ctt aaa ggc gtg gcg caa aac ttg aac aac cgc   1536
Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg
            500                 505                 510

atc gac aat gtg gac ggc aac gcg cgt gcg ggc atc gcc caa gcg att   1584
Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile
        515                 520                 525

gca acc gca ggt cta gtt cag gcg tat ctg ccc ggc aag agt atg atg   1632
Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met
    530                 535                 540

gcg atc ggc ggc gac act tat cgc ggc gaa gcc ggt tac gcc atc ggc   1680
Ala Ile Gly Gly Asp Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly
545                 550                 555                 560

tac tca agt att tcc gac ggc gga aat tgg att atc aaa ggc acg gct   1728
Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala
                565                 570                 575

tcc ggc aat tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat   1776
Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr
            580                 585                 590

caa tgg taa                                                     1785
Gln Trp
        595
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<210> 7
<211> 594
<212> PRT
<213> Neisseria meningitidis

<400> 7

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Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
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                20                  25                  30

Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
        35                  40                  45

Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
    50                  55                  60

Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
65                  70                  75                  80

Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
                85                  90                  95

Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Asp Ser Ser Phe Thr
        115                 120                 125

Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Glu Thr Glu
    130                 135                 140

Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp
145                 150                 155                 160

Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp
                165                 170                 175

Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu
            180                 185                 190

Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp
        195                 200                 205

Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly
    210                 215                 220

Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val
225                 230                 235                 240

Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr
                245                 250                 255

Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr
            260                 265                 270

Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly
        275                 280                 285

Lys Leu Val Thr Gly Lys Gly Lys Asp Glu Asn Gly Ser Ser Thr Asp
    290                 295                 300

Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn
305                 310                 315                 320

Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly
                325                 330                 335

Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe
            340                 345                 350

Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly
        355                 360                 365
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```
Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val
    370                 375                 380

Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala
385                 390                 395                 400

Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly
                405                 410                 415

Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile
            420                 425                 430

Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Ala Pro Gln
        435                 440                 445

Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser
    450                 455                 460

Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Thr Asn Lys
465                 470                 475                 480

Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val
                485                 490                 495

Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg
            500                 505                 510

Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile
        515                 520                 525

Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met
    530                 535                 540

Ala Ile Gly Gly Asp Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly
545                 550                 555                 560

Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala
                565                 570                 575

Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr
            580                 585                 590

Gln Trp
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<210> 8
<211> 1785
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1785)

<400> 8

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atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg   48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gcc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

acc gtg gcg acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag   144
Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
```

```
         35                  40                  45

gcg agt act acc gat gac gac gat tta tat tta gaa ccc gta caa cgc   192
Ala Ser Thr Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
     50                  55                  60

act gct gtc gtg ttg agc ttc cgt tcc gat aaa gaa ggc acg gga gaa   240
Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65                  70                  75                  80

aaa gaa gtt aca gaa gat tca aat tgg gga gta tat ttc gac aag aaa   288
Lys Glu Val Thr Glu Asp Ser Asn Trp Gly Val Tyr Phe Asp Lys Lys
                 85                  90                  95

gga gta cta aca gcc gga aca atc acc ctc aaa gcc ggc gac aac ctg   336
Gly Val Leu Thr Ala Gly Thr Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

aaa atc aaa caa aac acc aat gaa aac acc aat gcc agt agc ttc acc   384
Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr
        115                 120                 125

tac tcg ctg aaa aaa gac ctc aca gat ctg acc agt gtt gga act gaa   432
Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu
    130                 135                 140

aaa tta tcg ttt agc gca aac agc aat aaa gtc aac atc aca agc gac   480
Lys Leu Ser Phe Ser Ala Asn Ser Asn Lys Val Asn Ile Thr Ser Asp
145                 150                 155                 160

acc aaa ggc ttg aat ttc gcg aaa aaa acg gct gag acc aac ggc gac   528
Thr Lys Gly Leu Asn Phe Ala Lys Lys Thr Ala Glu Thr Asn Gly Asp
                165                 170                 175

acc acg gtt cat ctg aac ggt atc ggt tcg act ttg acc gat acg ctg   576
Thr Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu
            180                 185                 190

ctg aat acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat   624
Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp
        195                 200                 205

gac gag aaa aaa cgt gcg gca agc gtt aaa gac gta tta aac gca ggc   672
Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly
    210                 215                 220

tgg aac att aaa ggc gtt aaa ccc ggt aca aca gct tcc gat aac gtt   720
Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val
225                 230                 235                 240

gat ttc gtc cgc act tac gac aca gtc gag ttc ttg agc gca gat acg   768
Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr
                245                 250                 255

aaa aca acg act gtt aat gtg gaa agc aaa gac aac ggc aag aga acc   816
Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Arg Thr
            260                 265                 270

gaa gtt aaa atc ggt gcg aag act tct gtt atc aaa gaa aaa gac ggt   864
Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly
        275                 280                 285

aag ttg gtt act ggt aaa gac aaa ggc gag aat gat tct tct aca gac   912
Lys Leu Val Thr Gly Lys Asp Lys Gly Glu Asn Asp Ser Ser Thr Asp
    290                 295                 300
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```
aaa ggc gaa ggc tta gtg act gca aaa gaa gtg att gat gca gta aac   960
Lys Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn
305                 310                 315                 320

aag gct ggt tgg aga atg aaa aca aca acc gct aat ggt caa aca ggt  1008
Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly
                325                 330                 335

caa gct gac aag ttt gaa acc gtt aca tca ggc aca aat gta acc ttt  1056
Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe
            340                 345                 350

gct agt ggt aaa ggt aca act gcg act gta agt aaa gat gat caa ggc  1104
Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly
        355                 360                 365

aac atc act gtt atg tat gat gta aat gtc ggc gat gcc cta aac gtc  1152
Asn Ile Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val
    370                 375                 380

aat cag ctg caa aac agc ggt tgg aat ttg gat tcc aaa gcg gtt gca  1200
Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala
385                 390                 395                 400

ggt tct tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga  1248
Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly
                405                 410                 415

aag atg gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att  1296
Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile
            420                 425                 430

acc cgc aac ggc aaa aat atc gac atc gcc act tcg atg acc ccg caa  1344
Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln
        435                 440                 445

ttt tcc agc gtt tcg ctc ggc gcg ggg gcg gat gcg ccc act tta agc  1392
Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser
    450                 455                 460

gtg gat gac gag ggc gcg ttg aat gtc ggc agc aag gat gcc aac aaa  1440
Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys
465                 470                 475                 480

ccc gtc cgc att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt  1488
Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val
                485                 490                 495

aca aac gtc gca caa ctt aaa ggc gtg gcg caa aac ttg aac aac cac  1536
Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn His
            500                 505                 510

atc gac aat gtg gac ggc aac gcg cgt gcg ggc atc gcc caa gcg att  1584
Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile
        515                 520                 525

gca acc gca ggt ctg gtt cag gcg tat ctg ccc ggc aag agt atg atg  1632
Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met
    530                 535                 540

gcg atc ggc ggc ggc act tat cgc ggc gaa gcc ggt tat gcc atc ggc  1680
Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly
545                 550                 555                 560
```

```
tac tca agc att tcc gac ggc gga aat tgg att atc aaa ggc acg gct   1728
Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala
                565                 570                 575

tcc ggc aat tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat   1776
Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr
            580                 585                 590

cag tgg taa                                                       1785
Gln Trp
        595
```

<210> 9
<211> 594
<212> PRT
<213> Neisseria meningitidis

<400> 9

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Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

Ala Ser Thr Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
     50                  55                  60

Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65                  70                  75                  80

Lys Glu Val Thr Glu Asp Ser Asn Trp Gly Val Tyr Phe Asp Lys Lys
                 85                  90                  95

Gly Val Leu Thr Ala Gly Thr Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr
        115                 120                 125

Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu
    130                 135                 140

Lys Leu Ser Phe Ser Ala Asn Ser Asn Lys Val Asn Ile Thr Ser Asp
145                 150                 155                 160

Thr Lys Gly Leu Asn Phe Ala Lys Lys Thr Ala Glu Thr Asn Gly Asp
                165                 170                 175

Thr Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu
            180                 185                 190

Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp
        195                 200                 205

Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly
    210                 215                 220

Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val
225                 230                 235                 240

Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr
```

```
                245                 250                 255

Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Arg Thr
            260                 265                 270

Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly
        275                 280                 285

Lys Leu Val Thr Gly Lys Asp Lys Gly Glu Asn Asp Ser Ser Thr Asp
    290                 295                 300

Lys Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn
305                 310                 315                 320

Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly
                325                 330                 335

Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe
            340                 345                 350

Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly
        355                 360                 365

Asn Ile Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val
    370                 375                 380

Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala
385                 390                 395                 400

Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly
                405                 410                 415

Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile
            420                 425                 430

Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln
        435                 440                 445

Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser
    450                 455                 460

Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys
465                 470                 475                 480

Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val
                485                 490                 495

Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn His
            500                 505                 510

Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile
        515                 520                 525

Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met
    530                 535                 540

Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly
545                 550                 555                 560

Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala
                565                 570                 575

Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr
            580                 585                 590
```

Gln Trp

<210> 10
<211> 1776
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1776)

<400> 10

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atg aac gaa ata ttg cgc atc att tgg aat agc gcc ctc aat gcc tgg   48
Met Asn Glu Ile Leu Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gtt gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

acc gtg aag acc gcc gta ttg gcg act ctg ttg ttt gca acg gtt cag   144
Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

gca agt gct aac aat gaa gag caa gaa gaa gat tta tat tta gac ccc   192
Ala Ser Ala Asn Asn Glu Glu Gln Glu Glu Asp Leu Tyr Leu Asp Pro
     50                  55                  60

gtg cta cgc act gtt gcc gtg ttg ata gtc aat tcc gat aaa gaa ggc   240
Val Leu Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
 65                  70                  75                  80

acg gga gaa aaa gaa aaa gta gaa gaa aat tca gat tgg gca gta tat   288
Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
                 85                  90                  95

ttc aac gag aaa gga gta cta aca gcc aga gaa atc acc ctc aaa gcc   336
Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
            100                 105                 110

ggc gac aac ctg aaa atc aaa caa aac ggc aca aac ttc acc tac tcg   384
Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
        115                 120                 125

ctg aaa aaa gac ctc aca gat ctg acc agt gtt gga act gaa aaa tta   432
Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
    130                 135                 140

tcg ttt agc gca aac ggc aat aaa gtc aac atc aca agc gac acc aaa   480
Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
145                 150                 155                 160

ggc ttg aat ttt gcg aaa gaa acg gct ggg acg aac ggc gac acc acg   528
Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
                165                 170                 175

gtt cat ctg aac ggt att ggt tcg act ttg acc gat acg ctg ctg aat   576
Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
            180                 185                 190

acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat gac gag   624
Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
        195                 200                 205
```

```
aaa aaa cgt gcg gca agc gtt aaa gac gta tta aac gct ggc tgg aac   672
Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
    210                 215                 220

att aaa ggc gtt aaa ccc ggt aca aca gct tcc gat aac gtt gat ttc   720
Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
225                 230                 235                 240

gtc cgc act tac gac aca gtc gag ttc ttg agc gca gat acg aaa aca   768
Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
                245                 250                 255

acg act gtt aat gtg gaa agc aaa gac aac ggc aag aaa acc gaa gtt   816
Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
            260                 265                 270

aaa atc ggt gcg aag act tct gtt att aaa gaa aaa gac ggt aag ttg   864
Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
        275                 280                 285

gtt act ggt aaa gac aaa ggc gag aat ggt tct tct aca gac gaa ggc   912
Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
    290                 295                 300

gaa ggc tta gtg act gca aaa gaa gtg att gat gca gta aac aag gct   960
Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
305                 310                 315                 320

ggt tgg aga atg aaa aca aca acc gct aat ggt caa aca ggt caa gct  1008
Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
                325                 330                 335

gac aag ttt gaa acc gtt aca tca ggc aca aat gta acc ttt gct agt  1056
Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser
            340                 345                 350

ggt aaa ggt aca act gcg act gta agt aaa gat gat caa ggc aac atc  1104
Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
        355                 360                 365

act gtt atg tat gat gta aat gtc ggc gat gcc cta aac gtc aat cag  1152
Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
    370                 375                 380

ctg caa aac agc ggt tgg aat ttg gat tcc aaa gcg gtt gca ggt tct  1200
Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
385                 390                 395                 400

tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga aag atg  1248
Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
                405                 410                 415

gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att acc cgc  1296
Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
            420                 425                 430

aac ggt aaa aat atc gac atc gcc act tcg atg acc ccg cag ttt tcc  1344
Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
        435                 440                 445

agc gtt tcg ctc ggc gcg ggg gcg gat gcg ccc act ttg agc gtg gat  1392
Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
    450                 455                 460

ggg gac gca ttg aat gtc ggc agc aag aag gac aac aaa ccc gtc cgc  1440
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```
Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg
465                 470                 475                 480

att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac gtc   1488
Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val
                485                 490                 495

gca caa ctt aaa ggc gtg gcg caa aac ttg aac aac cgc atc gac aat   1536
Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn
            500                 505                 510

gtg gac ggc aac gcg cgt gcg ggc atc gcc caa gcg att gca acc gca   1584
Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala
        515                 520                 525

ggt ctg gtt cag gcg tat ttg ccc ggc aag agt atg atg gcg atc ggc   1632
Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly
    530                 535                 540

ggc ggc act tat cgc ggc gaa gcc ggt tac gcc atc ggc tac tcc agt   1680
Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser
545                 550                 555                 560

att tcc gac ggc gga aat tgg att atc aaa ggc acg gct tcc ggc aat   1728
Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn
                565                 570                 575

tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat cag tgg taa   1776
Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
            580                 585                 590
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<210> 11
<211> 591
<212> PRT
<213> Neisseria meningitidis

<400> 11

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Met Asn Glu Ile Leu Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

Ala Ser Ala Asn Asn Glu Glu Gln Glu Glu Asp Leu Tyr Leu Asp Pro
     50                  55                  60

Val Leu Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
 65                  70                  75                  80

Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
                 85                  90                  95

Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
            100                 105                 110

Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
        115                 120                 125

Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
    130                 135                 140
```

Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
145 150 155 160

Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
165 170 175

Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
180 185 190

Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
195 200 205

Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
210 215 220

Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
225 230 235 240

Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
245 250 255

Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
260 265 270

Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
275 280 285

Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
290 295 300

Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
305 310 315 320

Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
325 330 335

Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser
340 345 350

Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
355 360 365

Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
370 375 380

Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
385 390 395 400

Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
405 410 415

Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
420 425 430

Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
435 440 445

Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
450 455 460

Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg
465 470 475 480

Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val
485 490 495

```
Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn
            500                 505                 510

Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala
        515                 520                 525

Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly
    530                 535                 540

Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser
545                 550                 555                 560

Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn
                565                 570                 575

Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
            580                 585                 590


<210> 12
<211> 1797
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1797)

<400> 12
atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg   48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
            20                  25                  30

acc gtg gcg acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag   144
Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
        35                  40                  45

gcg aat gct acc gat gac gac gat tta tat tta gaa ccc gta caa cgc   192
Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
    50                  55                  60

act gct gtc gtg ttg agc ttc cgt tcc gat aaa gaa ggc acg gga gaa   240
Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
65                  70                  75                  80

aaa gaa ggt aca gaa gat tca aat tgg gca gta tat ttc gac gag aaa   288
Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
                85                  90                  95

aga gta cta aaa gcc gga gca atc acc ctc aaa gcc ggc gac aac ctg   336
Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

aaa atc aaa caa aac acc aat gaa aac acc aat gaa aac acc aat gac   384
Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Glu Asn Thr Asn Asp
        115                 120                 125

agt agc ttc acc tac tcc ctg aaa aaa gac ctc aca gat ctg acc agt   432
Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser
    130                 135                 140
```

```
gtt gaa act gaa aaa tta tcg ttt ggc gca aac ggt aat aaa gtc aac   480
Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn
145                 150                 155                 160

atc aca agc gac acc aaa ggc ttg aat ttt gcg aaa gaa acg gct ggg   528
Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
                165                 170                 175

acg aac ggc gac ccc acg gtt cat ctg aac ggt atc ggt tcg act ttg   576
Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
            180                 185                 190

acc gat acg ctg ctg aat acc gga gcg acc aca aac gta acc aac gac   624
Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
        195                 200                 205

aac gtt acc gat gac gag aaa aaa cgt gcg gca agc gtt aaa gac gta   672
Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
    210                 215                 220

tta aac gca ggc tgg aac att aaa ggc gtt aaa ccc ggt aca aca gct   720
Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala
225                 230                 235                 240

tcc gat aac gtt gat ttc gtc cgc act tac gac aca gtc gag ttc ttg   768
Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu
                245                 250                 255

agc gca gat acg aaa aca acg act gtt aat gtg gaa agc aaa gac aac   816
Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn
            260                 265                 270

ggc aag aaa acc gaa gtt aaa atc ggt gcg aag act tct gtt att aaa   864
Gly Lys Lys Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys
        275                 280                 285

gaa aaa gac ggt aag ttg gtt act ggt aaa ggc aaa gac gag aat ggt   912
Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Asp Glu Asn Gly
    290                 295                 300

tct tct aca gac gaa ggc gaa ggc tta gtg act gca aaa gaa gtg att   960
Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile
305                 310                 315                 320

gat gca gta aac aag gct ggt tgg aga atg aaa aca aca acc gct aat  1008
Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn
                325                 330                 335

ggt caa aca ggt caa gct gac aag ttt gaa acc gtt aca tca ggc aca  1056
Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr
            340                 345                 350

aaa gta acc ttt gct agt ggt aat ggt aca act gcg act gta agt aaa  1104
Lys Val Thr Phe Ala Ser Gly Asn Gly Thr Thr Ala Thr Val Ser Lys
        355                 360                 365

gat gat caa ggc aac atc act gtt aag tat gat gta aat gtc ggc gat  1152
Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp
    370                 375                 380

gcc cta aac gtc aat cag ctg caa aac agc ggt tgg aat ttg gat tcc  1200
Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser
385                 390                 395                 400
```

```
aaa gcg gtt gca ggt tct tcg ggc aaa gtc atc agc ggc aat gtt tcg   1248
Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser
                405                 410                 415

ccg agc aag gga aag atg gat gaa acc gtc aac att aat gcc ggc aac   1296
Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn
            420                 425                 430

aac atc gag att acc cgc aac ggc aaa aat atc gac atc gcc act tcg   1344
Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser
        435                 440                 445

atg acc ccg caa ttt tcc agc gtt tcg ctc ggc gcg ggg gcg gat gcg   1392
Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala
    450                 455                 460

ccc act tta agc gtg gat gac gag ggc gcg ttg aat gtc ggc agc aag   1440
Pro Thr Leu Ser Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys
465                 470                 475                 480

gat gcc aac aaa ccc gtc cgc att acc aat gtc gcc ccg ggc gtt aaa   1488
Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys
                485                 490                 495

gag ggg gat gtt aca aac gtc gca caa ctt aaa ggt gtg gcg caa aac   1536
Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn
            500                 505                 510

ttg aac aac cgc atc gac aat gtg gac ggc aac gcg cgc gcg ggt atc   1584
Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile
        515                 520                 525

gcc caa gcg att gca acc gca ggt ttg gct cag gcg tat ttg ccc ggc   1632
Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly
    530                 535                 540

aag agt atg atg gcg atc ggc ggc ggt act tat cgc ggc gaa gcc ggt   1680
Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly
545                 550                 555                 560

tac gcc atc ggc tac tcg agc att tct gac act ggg aat tgg gtt atc   1728
Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile
                565                 570                 575

aag ggc acg gct tcc ggc aat tcg cgc ggc cat ttc ggt gct tcc gca   1776
Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala
            580                 585                 590

tct gtc ggt tat cag tgg taa                                      1797
Ser Val Gly Tyr Gln Trp
        595
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<210> 13
<211> 598
<212> PRT
<213> Neisseria meningitidis

<400> 13

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Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30
```

```
Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
          35                  40                  45

Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
     50                  55                  60

Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65                  70                  75                  80

Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
                 85                  90                  95

Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
            100                 105                 110

Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Glu Asn Thr Asn Asp
        115                 120                 125

Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser
    130                 135                 140

Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn
145                 150                 155                 160

Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
                165                 170                 175

Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
            180                 185                 190

Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
        195                 200                 205

Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
    210                 215                 220

Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala
225                 230                 235                 240

Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu
                245                 250                 255

Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn
            260                 265                 270

Gly Lys Lys Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys
        275                 280                 285

Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Asp Glu Asn Gly
    290                 295                 300

Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile
305                 310                 315                 320

Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn
                325                 330                 335

Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr
            340                 345                 350

Lys Val Thr Phe Ala Ser Gly Asn Gly Thr Thr Ala Thr Val Ser Lys
        355                 360                 365

Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp
    370                 375                 380
```

```
Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser
385                 390                 395                 400

Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser
                405                 410                 415

Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn
            420                 425                 430

Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser
        435                 440                 445

Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala
    450                 455                 460

Pro Thr Leu Ser Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys
465                 470                 475                 480

Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys
                485                 490                 495

Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn
            500                 505                 510

Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile
        515                 520                 525

Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly
    530                 535                 540

Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly
545                 550                 555                 560

Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile
                565                 570                 575

Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala
            580                 585                 590

Ser Val Gly Tyr Gln Trp
        595
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<210> 14
<211> 1800
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1800)

<400> 14

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atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg   48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gcc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

acc gtg aag acc gcc gta ttg gcg acg ctg ttg ttt gca acg gtt cag   144
Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45
```

```
gcg aat gct acc gat gaa gat gaa gaa gaa gag tta gaa ccc gta gta   192
Ala Asn Ala Thr Asp Glu Asp Glu Glu Glu Glu Leu Glu Pro Val Val
     50                  55                  60

cgc tct gct ctg gtg ttg caa ttc atg atc gat aaa gaa ggc aat gga   240
Arg Ser Ala Leu Val Leu Gln Phe Met Ile Asp Lys Glu Gly Asn Gly
 65                  70                  75                  80

gaa aac gaa tct aca gga aat ata ggt tgg agt ata tat tac gac aat   288
Glu Asn Glu Ser Thr Gly Asn Ile Gly Trp Ser Ile Tyr Tyr Asp Asn
                 85                  90                  95

cac aac act cta cac ggc gca acc gtt acc ctc aaa gcc ggc gac aac   336
His Asn Thr Leu His Gly Ala Thr Val Thr Leu Lys Ala Gly Asp Asn
            100                 105                 110

ctg aaa atc aaa caa aac acc aat aaa aac acc aat gaa aac acc aat   384
Leu Lys Ile Lys Gln Asn Thr Asn Lys Asn Thr Asn Glu Asn Thr Asn
        115                 120                 125

gac agt agc ttc acc tac tcg ctg aaa aaa gac ctc aca gat ctg acc   432
Asp Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr
    130                 135                 140

agt gtt gaa act gaa aaa tta tcg ttt ggc gca aac ggc aat aaa gtc   480
Ser Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val
145                 150                 155                 160

aac atc aca agc gac acc aaa ggc ttg aat ttc gcg aaa gaa acg gct   528
Asn Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala
                165                 170                 175

ggg acg aac ggc gac acc acg gtt cat ctg aac ggt att ggt tcg act   576
Gly Thr Asn Gly Asp Thr Thr Val His Leu Asn Gly Ile Gly Ser Thr
            180                 185                 190

ttg acc gat acg ctg ctg aat acc gga gcg acc aca aac gta acc aac   624
Leu Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn
        195                 200                 205

gac aac gtt acc gat gac aag aaa aaa cgt gcg gca agc gtt aaa gac   672
Asp Asn Val Thr Asp Asp Lys Lys Lys Arg Ala Ala Ser Val Lys Asp
    210                 215                 220

gta tta aac gca ggc tgg aac att aaa ggc gtt aaa ccc ggt aca aca   720
Val Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr
225                 230                 235                 240

gct tcc gat aac gtt gat ttc gtc cac act tac gac aca gtc gag ttc   768
Ala Ser Asp Asn Val Asp Phe Val His Thr Tyr Asp Thr Val Glu Phe
                245                 250                 255

ttg agc gca gat acg aaa aca acg act gtt aat gtg gaa agc aaa gac   816
Leu Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp
            260                 265                 270

aac ggc aag aga acc gaa gtt aaa atc ggt gcg aag act tct gtt att   864
Asn Gly Lys Arg Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile
        275                 280                 285

aaa gaa aaa gac ggt aag ttg gtt act ggt aaa ggc aaa ggc gag aat   912
Lys Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Gly Glu Asn
    290                 295                 300
```

```
ggt tct tct aca gac gaa ggc gaa ggc tta gtg act gca aaa gaa gtg   960
Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val
305                 310                 315                 320

att gat gca gta aac aag gct ggt tgg aga atg aaa aca aca acc gct  1008
Ile Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala
                325                 330                 335

aat ggt caa aca ggt caa gct gac aag ttt gaa acc gtt aca tca ggc  1056
Asn Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly
            340                 345                 350

aca aat gta acc ttt gct agt ggt aaa ggt aca act gcg act gta agt  1104
Thr Asn Val Thr Phe Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser
        355                 360                 365

aaa gat gat caa ggc aac atc act gtt aag tat gat gta aat gtc ggc  1152
Lys Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly
    370                 375                 380

gat gcc cta aac gtc aat cag ctg caa aac agc ggt tgg aat ttg gat  1200
Asp Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp
385                 390                 395                 400

tcc aaa gcg gtt gca ggt tct tcg ggc aaa gtc atc agc ggc aat gtt  1248
Ser Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val
                405                 410                 415

tcg ccg agc aag gga aag atg gat gaa acc gtc aac att aat gcc ggc  1296
Ser Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly
            420                 425                 430

aac aac atc gag att acc cgc aac ggt aaa aat atc gac atc gcc act  1344
Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr
        435                 440                 445

tcg atg acc ccg cag ttt tcc agc gtt tcg ctc ggc gcg ggg gcg gat  1392
Ser Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp
    450                 455                 460

gcg ccc act ttg agc gtg gat gac aag ggc gcg ttg aat gtc ggc agc  1440
Ala Pro Thr Leu Ser Val Asp Asp Lys Gly Ala Leu Asn Val Gly Ser
465                 470                 475                 480

aag gat gcc aac aaa ccc gtc cgc att acc aat gtc gcc ccg ggc gtt  1488
Lys Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val
                485                 490                 495

aaa gag ggg gat gtt aca aac gtc gca caa ctt aaa ggc gtg gcg caa  1536
Lys Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln
            500                 505                 510

aac ttg aac aac cgc atc gac aat gtg gac ggc aac gcg cgt gcg ggc  1584
Asn Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly
        515                 520                 525

atc gcc caa gcg att gca acc gca ggt ctg gtt cag gcg tat ctg ccc  1632
Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro
    530                 535                 540

ggc aag agt atg atg gcg atc ggc ggc ggc act tat cgc ggc gaa gcc  1680
Gly Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala
545                 550                 555                 560

ggt tac gcc atc ggc tac tcc agt att tcc gac ggc gga aat tgg att  1728
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Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile
                565                 570                 575

atc aaa ggc acg gct tcc ggc aat tcg cgc ggt cat ttc ggt gct tcc   1776
Ile Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser
            580                 585                 590

gca tct gtc ggt tat cag tgg taa                                   1800
Ala Ser Val Gly Tyr Gln Trp
        595                 600
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<210> 15
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<213> Neisseria meningitidis

<400> 15

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Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

Ala Asn Ala Thr Asp Glu Asp Glu Glu Glu Leu Glu Pro Val Val
     50                  55                  60

Arg Ser Ala Leu Val Leu Gln Phe Met Ile Asp Lys Glu Gly Asn Gly
 65                  70                  75                  80

Glu Asn Glu Ser Thr Gly Asn Ile Gly Trp Ser Ile Tyr Tyr Asp Asn
                 85                  90                  95

His Asn Thr Leu His Gly Ala Thr Val Thr Leu Lys Ala Gly Asp Asn
            100                 105                 110

Leu Lys Ile Lys Gln Asn Thr Asn Lys Asn Thr Asn Glu Asn Thr Asn
        115                 120                 125

Asp Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr
    130                 135                 140

Ser Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val
145                 150                 155                 160

Asn Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala
                165                 170                 175

Gly Thr Asn Gly Asp Thr Thr Val His Leu Asn Gly Ile Gly Ser Thr
            180                 185                 190

Leu Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn
        195                 200                 205

Asp Asn Val Thr Asp Asp Lys Lys Lys Arg Ala Ala Ser Val Lys Asp
    210                 215                 220

Val Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr
225                 230                 235                 240

Ala Ser Asp Asn Val Asp Phe Val His Thr Tyr Asp Thr Val Glu Phe
                245                 250                 255
```

Leu Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp
260 265 270

Asn Gly Lys Arg Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile
275 280 285

Lys Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Gly Glu Asn
290 295 300

Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val
305 310 315 320

Ile Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala
325 330 335

Asn Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly
340 345 350

Thr Asn Val Thr Phe Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser
355 360 365

Lys Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly
370 375 380

Asp Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp
385 390 395 400

Ser Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val
405 410 415

Ser Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly
420 425 430

Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr
435 440 445

Ser Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp
450 455 460

Ala Pro Thr Leu Ser Val Asp Asp Lys Gly Ala Leu Asn Val Gly Ser
465 470 475 480

Lys Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val
485 490 495

Lys Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln
500 505 510

Asn Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly
515 520 525

Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro
530 535 540

Gly Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala
545 550 555 560

Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile
565 570 575

Ile Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser
580 585 590

Ala Ser Val Gly Tyr Gln Trp

595

<210> 16
<211> 1779
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1779)

<400> 16

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atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg   48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gcc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

acc gtg aag acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag   144
Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

gcg aat gct acc gat gaa gat gaa gaa gaa gag tta gaa tcc gta caa   192
Ala Asn Ala Thr Asp Glu Asp Glu Glu Glu Leu Glu Ser Val Gln
     50                  55                  60

cgc tct gtc gta ggg agc att caa gcc agt atg gaa ggc agc gtc gaa   240
Arg Ser Val Val Gly Ser Ile Gln Ala Ser Met Glu Gly Ser Val Glu
 65                  70                  75                  80

ttg gaa acg ata tca tta tca atg act aac gac agc aag gaa ttt gta   288
Leu Glu Thr Ile Ser Leu Ser Met Thr Asn Asp Ser Lys Glu Phe Val
                 85                  90                  95

gac cca tac ata gta gtt acc ctc aaa gcc ggc gac aac ctg aaa atc   336
Asp Pro Tyr Ile Val Val Thr Leu Lys Ala Gly Asp Asn Leu Lys Ile
            100                 105                 110

aaa caa aac acc aat gaa aac acc aat gcc agt agc ttc acc tac tcg   384
Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr Tyr Ser
        115                 120                 125

ctg aaa aaa gac ctc aca ggc ctg atc aat gtt gaa act gaa aaa tta   432
Leu Lys Lys Asp Leu Thr Gly Leu Ile Asn Val Glu Thr Glu Lys Leu
    130                 135                 140

tcg ttt ggc gca aac ggc aag aaa gtc aac atc ata agc gac acc aaa   480
Ser Phe Gly Ala Asn Gly Lys Lys Val Asn Ile Ile Ser Asp Thr Lys
145                 150                 155                 160

ggc ttg aat ttc gcg aaa gaa acg gct ggg acg aac ggc gac acc acg   528
Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
                165                 170                 175

gtt cat ctg aac ggt atc ggt tcg act ttg acc gat atg ctg ctg aat   576
Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Met Leu Leu Asn
            180                 185                 190

acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat gac gag   624
Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
        195                 200                 205
```

```
aaa aaa cgt gcg gca agc gtt aaa gac gta tta aac gca ggc tgg aac   672
Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
    210                 215                 220

att aaa ggc gtt aaa ccc ggt aca aca gct tcc gat aac gtt gat ttc   720
Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
225                 230                 235                 240

gtc cgc act tac gac aca gtc gag ttc ttg agc gca gat acg aaa aca   768
Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
                245                 250                 255

acg act gtt aat gtg gaa agc aaa gac aac ggc aag aaa acc gaa gtt   816
Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
            260                 265                 270

aaa atc ggt gcg aag act tct gtt att aaa gaa aaa gac ggt aag ttg   864
Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
        275                 280                 285

gtt act ggt aaa ggc aaa ggc gag aat ggt tct tct aca gac gaa ggc   912
Val Thr Gly Lys Gly Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
    290                 295                 300

gaa ggc tta gtg act gca aaa gaa gtg att gat gca gta aac aag gct   960
Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
305                 310                 315                 320

ggt tgg aga atg aaa aca aca acc gct aat ggt caa aca ggt caa gct  1008
Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
                325                 330                 335

gac aag ttt gaa acc gtt aca tca ggc aca aaa gta acc ttt gct agt  1056
Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Lys Val Thr Phe Ala Ser
            340                 345                 350

ggt aat ggt aca act gcg act gta agt aaa gat gat caa ggc aac atc  1104
Gly Asn Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
        355                 360                 365

act gtt aag tat gat gta aat gtc ggc gat gcc cta aac gtc aat cag  1152
Thr Val Lys Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
    370                 375                 380

ctg caa aac agc ggt tgg aat ttg gat tcc aaa gcg gtt gca ggt tct  1200
Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
385                 390                 395                 400

tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga aag atg  1248
Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
                405                 410                 415

gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att acc cgc  1296
Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
            420                 425                 430

aac ggc aaa aat atc gac atc gcc act tcg atg acc ccg caa ttt tcc  1344
Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
        435                 440                 445

agc gtt tcg ctc ggc gcg ggg gcg gat gcg ccc act tta agc gtg gat  1392
Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
    450                 455                 460

gac gag ggc gcg ttg aat gtc ggc agc aag gat gcc aac aaa ccc gtc  1440
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```
Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val
465                 470                 475                 480

cgc att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac   1488
Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn
                485                 490                 495

gtc gcg caa ctt aaa ggt gtg gcg caa aac ttg aac aac cgc atc gac   1536
Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp
            500                 505                 510

aat gtg aac ggc aac gcg cgt gcg ggc atc gcc caa gcg att gca acc   1584
Asn Val Asn Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr
        515                 520                 525

gca ggt ctg gtt cag gcg tat ctg ccc ggc aag agt atg atg gcg atc   1632
Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile
    530                 535                 540

ggc ggc ggc act tat ctc ggc gaa gcc ggt tat gcc atc ggc tac tca   1680
Gly Gly Gly Thr Tyr Leu Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser
545                 550                 555                 560

agc att tcc gcc ggc gga aat tgg att atc aaa ggc acg gct tcc ggc   1728
Ser Ile Ser Ala Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly
                565                 570                 575

aat tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat cag tgg   1776
Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
            580                 585                 590

taa                                                               1779
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<210> 17
<211> 592
<212> PRT
<213> Neisseria meningitidis

<400> 17

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Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

Ala Asn Ala Thr Asp Glu Asp Glu Glu Glu Leu Glu Ser Val Gln
     50                  55                  60

Arg Ser Val Val Gly Ser Ile Gln Ala Ser Met Glu Gly Ser Val Glu
 65                  70                  75                  80

Leu Glu Thr Ile Ser Leu Ser Met Thr Asn Asp Ser Lys Glu Phe Val
                 85                  90                  95

Asp Pro Tyr Ile Val Val Thr Leu Lys Ala Gly Asp Asn Leu Lys Ile
            100                 105                 110

Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr Tyr Ser
        115                 120                 125
```

Leu Lys Lys Asp Leu Thr Gly Leu Ile Asn Val Glu Thr Glu Lys Leu
130 135 140

Ser Phe Gly Ala Asn Gly Lys Lys Val Asn Ile Ile Ser Asp Thr Lys
145 150 155 160

Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
165 170 175

Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Met Leu Leu Asn
180 185 190

Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
195 200 205

Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
210 215 220

Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
225 230 235 240

Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
245 250 255

Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
260 265 270

Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
275 280 285

Val Thr Gly Lys Gly Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
290 295 300

Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
305 310 315 320

Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
325 330 335

Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Lys Val Thr Phe Ala Ser
340 345 350

Gly Asn Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
355 360 365

Thr Val Lys Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
370 375 380

Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
385 390 395 400

Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
405 410 415

Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
420 425 430

Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
435 440 445

Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
450 455 460

Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val
465 470 475 480

```
Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn
                485                 490                 495

Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp
            500                 505                 510

Asn Val Asn Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr
        515                 520                 525

Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile
    530                 535                 540

Gly Gly Gly Thr Tyr Leu Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser
545                 550                 555                 560

Ser Ile Ser Ala Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly
                565                 570                 575

Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
            580                 585                 590
```

<210> 18
<211> 1770
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1770)

<400> 18

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atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg   48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gta gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

acc gtg gcg acc gcc gta ttg gcg aca ctg ctg tcc gca acg gtt cag   144
Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Ser Ala Thr Val Gln
         35                  40                  45

gcg aat gct acc gat acc gat gaa gat gaa gag tta gaa tcc gta gca   192
Ala Asn Ala Thr Asp Thr Asp Glu Asp Glu Glu Leu Glu Ser Val Ala
     50                  55                  60

cgc tct gct ctg gtg ttg caa ttc atg atc gat aaa gaa ggc aat gga   240
Arg Ser Ala Leu Val Leu Gln Phe Met Ile Asp Lys Glu Gly Asn Gly
 65                  70                  75                  80

gaa atc gaa tct aca gga gat ata ggt tgg agt ata tat tac gac gat   288
Glu Ile Glu Ser Thr Gly Asp Ile Gly Trp Ser Ile Tyr Tyr Asp Asp
                 85                  90                  95

cac aac act cta cac ggc gca acc gtt acc ctc aaa gcc ggc gac aac   336
His Asn Thr Leu His Gly Ala Thr Val Thr Leu Lys Ala Gly Asp Asn
            100                 105                 110

ctg aaa atc aaa caa agc ggc aaa gac ttc acc tac tcg ctg aaa aaa   384
Leu Lys Ile Lys Gln Ser Gly Lys Asp Phe Thr Tyr Ser Leu Lys Lys
        115                 120                 125
```

```
gag ctg aaa gac ctg acc agt gtt gaa act gaa aaa tta tcg ttt ggc   432
Glu Leu Lys Asp Leu Thr Ser Val Glu Thr Glu Lys Leu Ser Phe Gly
    130                 135                 140

gca aac ggt aat aaa gtc aac atc aca agc gac acc aaa ggc ttg aat   480
Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys Gly Leu Asn
145                 150                 155                 160

ttt gcg aaa gaa acg gct ggg acg aac ggc gac ccc acg gtt cat ctg   528
Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Pro Thr Val His Leu
                165                 170                 175

aac ggt atc ggt tcg act ttg acc gat acg ctt gcg ggt tct tct gct   576
Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Ala Gly Ser Ser Ala
            180                 185                 190

tct cac gtt gat gcg ggt aac caa agt aca cat tac act cgt gca gca   624
Ser His Val Asp Ala Gly Asn Gln Ser Thr His Tyr Thr Arg Ala Ala
        195                 200                 205

agt att aag gat gtg ttg aat gcg ggt tgg aat att aag ggt gtt aaa   672
Ser Ile Lys Asp Val Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys
    210                 215                 220

act ggc tca aca act ggt caa tca gaa aat gtc gat ttc gtc cgc act   720
Thr Gly Ser Thr Thr Gly Gln Ser Glu Asn Val Asp Phe Val Arg Thr
225                 230                 235                 240

tac gac aca gtc gag ttc ttg agc gca gat acg aaa aca acg act gtt   768
Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr Thr Thr Val
                245                 250                 255

aat gtg gaa agc aaa gac aac ggc aag aga acc gaa gtt aaa atc ggt   816
Asn Val Glu Ser Lys Asp Asn Gly Lys Arg Thr Glu Val Lys Ile Gly
            260                 265                 270

gcg aag act tct gtt att aaa gaa aaa gac ggt aag ttg gtt act ggt   864
Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu Val Thr Gly
        275                 280                 285

aaa ggc aaa ggc gag aat ggt tct tct aca gac gaa ggc gaa ggc tta   912
Lys Gly Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu
    290                 295                 300

gtg act gca aaa gaa gtg att gat gca gta aac aag gct ggt tgg aga   960
Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala Gly Trp Arg
305                 310                 315                 320

atg aaa aca aca acc gct aat ggt caa aca ggt caa gct gac aag ttt  1008
Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala Asp Lys Phe
                325                 330                 335

gaa acc gtt aca tca ggc aca aaa gta acc ttt gct agt ggt aat ggt  1056
Glu Thr Val Thr Ser Gly Thr Lys Val Thr Phe Ala Ser Gly Asn Gly
            340                 345                 350

aca act gcg act gta agt aaa gat gat caa ggc aac atc act gtt aag  1104
Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile Thr Val Lys
        355                 360                 365

tat gat gta aat gtc ggc gat gcc cta aac gtc aat cag ctg caa aac  1152
Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln Leu Gln Asn
    370                 375                 380

agc ggt tgg aat ttg gat tcc aaa gcg gtt gca ggt tct tcg ggc aaa  1200
```

```
Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser Ser Gly Lys
385                 390                 395                 400

gtc atc agc ggc aat gtt tcg ccg agc aag gga aag atg gat gaa acc   1248
Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met Asp Glu Thr
                405                 410                 415

gtc aac att aat gcc ggc aac aac atc gag att acc cgc aac ggc aaa   1296
Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys
            420                 425                 430

aat atc gac atc gcc act tcg atg acc ccg caa ttt tcc agc gtt tcg   1344
Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser Ser Val Ser
        435                 440                 445

ctc ggc gcg ggg gcg gat gcg ccc act tta agc gtg gat gac gag ggc   1392
Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp Asp Glu Gly
    450                 455                 460

gcg ttg aat gtc ggc agc aag gat gcc aac aaa ccc gtc cgc att acc   1440
Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val Arg Ile Thr
465                 470                 475                 480

aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac gtc gca caa   1488
Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val Ala Gln
                485                 490                 495

ctt aaa ggt gtg gcg caa aac ttg aac aac cgc atc gac aat gtg aac   1536
Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn Val Asn
            500                 505                 510

ggc aac gcg cgc gcg ggt atc gcc caa gcg att gca acc gca ggt ttg   1584
Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu
        515                 520                 525

gct cag gcc tat ttg ccc ggc aag agt atg atg gcg atc ggc ggc ggt   1632
Ala Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly Gly Gly
    530                 535                 540

act tat ctc ggc gaa gcc ggt tac gcc atc ggc tac tcg agc att tct   1680
Thr Tyr Leu Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser
545                 550                 555                 560

gac act ggg aat tgg gtt atc aag ggc acg gct tcc ggc aat tcg cgc   1728
Asp Thr Gly Asn Trp Val Ile Lys Gly Thr Ala Ser Gly Asn Ser Arg
                565                 570                 575

ggt cat ttc ggt act tcc gca tct gtc ggt tat cag tgg taa           1770
Gly His Phe Gly Thr Ser Ala Ser Val Gly Tyr Gln Trp
            580                 585                 590
```

<210> 19
<211> 589
<212> PRT
<213> Neisseria meningitidis

<400> 19

```
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Ser Ala Thr Val Gln
```

```
         35                  40                  45

Ala Asn Ala Thr Asp Thr Asp Glu Asp Glu Glu Leu Glu Ser Val Ala
     50                  55                  60

Arg Ser Ala Leu Val Leu Gln Phe Met Ile Asp Lys Glu Gly Asn Gly
 65                  70                  75                  80

Glu Ile Glu Ser Thr Gly Asp Ile Gly Trp Ser Ile Tyr Tyr Asp Asp
                 85                  90                  95

His Asn Thr Leu His Gly Ala Thr Val Thr Leu Lys Ala Gly Asp Asn
            100                 105                 110

Leu Lys Ile Lys Gln Ser Gly Lys Asp Phe Thr Tyr Ser Leu Lys Lys
        115                 120                 125

Glu Leu Lys Asp Leu Thr Ser Val Glu Thr Glu Lys Leu Ser Phe Gly
    130                 135                 140

Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys Gly Leu Asn
145                 150                 155                 160

Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Pro Thr Val His Leu
                165                 170                 175

Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Ala Gly Ser Ser Ala
            180                 185                 190

Ser His Val Asp Ala Gly Asn Gln Ser Thr His Tyr Thr Arg Ala Ala
        195                 200                 205

Ser Ile Lys Asp Val Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys
    210                 215                 220

Thr Gly Ser Thr Thr Gly Gln Ser Glu Asn Val Asp Phe Val Arg Thr
225                 230                 235                 240

Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr Thr Thr Val
                245                 250                 255

Asn Val Glu Ser Lys Asp Asn Gly Lys Arg Thr Glu Val Lys Ile Gly
            260                 265                 270

Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu Val Thr Gly
        275                 280                 285

Lys Gly Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu
    290                 295                 300

Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala Gly Trp Arg
305                 310                 315                 320

Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala Asp Lys Phe
                325                 330                 335

Glu Thr Val Thr Ser Gly Thr Lys Val Thr Phe Ala Ser Gly Asn Gly
            340                 345                 350

Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile Thr Val Lys
        355                 360                 365

Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln Leu Gln Asn
    370                 375                 380
```

```
Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser Ser Gly Lys
385                 390                 395                 400

Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met Asp Glu Thr
                405                 410                 415

Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys
            420                 425                 430

Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser Ser Val Ser
        435                 440                 445

Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp Asp Glu Gly
    450                 455                 460

Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val Arg Ile Thr
465                 470                 475                 480

Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val Ala Gln
                485                 490                 495

Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn Val Asn
            500                 505                 510

Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu
        515                 520                 525

Ala Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly Gly Gly
    530                 535                 540

Thr Tyr Leu Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser
545                 550                 555                 560

Asp Thr Gly Asn Trp Val Ile Lys Gly Thr Ala Ser Gly Asn Ser Arg
                565                 570                 575

Gly His Phe Gly Thr Ser Ala Ser Val Gly Tyr Gln Trp
            580                 585


<210> 20
<211> 1776
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1776)

<400> 20
atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gca tgg   48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

gtc gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca   96
Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

acc gtg aag acc gcc gta ttg gcg act ctg ttg ttt gca acg gtt cag   144
Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

gca agt gct aac aat gaa gag caa gaa gaa gat tta tat tta gac ccc   192
Ala Ser Ala Asn Asn Glu Glu Gln Glu Glu Asp Leu Tyr Leu Asp Pro
     50                  55                  60
```

```
gta caa cgc act gtt gcc gtg ttg ata gtc aat tcc gat aaa gaa ggc   240
Val Gln Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
 65                  70                  75                  80

acg gga gaa aaa gaa aaa gta gaa gaa aat tca gat tgg gca gta tat   288
Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
                 85                  90                  95

ttc aac gag aaa gga gta cta aca gcc aga gaa atc acc ctc aaa gcc   336
Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
            100                 105                 110

ggc gac aac ctg aaa atc aaa caa aac ggc aca aac ttc acc tac tcg   384
Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
        115                 120                 125

ctg aaa aaa gac ctc aca gat ctg acc agt gtt gga act gaa aaa tta   432
Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
    130                 135                 140

tcg ttt agc gca aac ggc aat aaa gtc aac atc aca agc gac acc aaa   480
Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
145                 150                 155                 160

ggc ttg aat ttt gcg aaa gaa acg gct ggg acg aac ggc gac acc acg   528
Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
                165                 170                 175

gtt cat ctg aac ggt att ggt tcg act ttg acc gat acg ctg ctg aat   576
Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
            180                 185                 190

acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat gac gag   624
Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
        195                 200                 205

aaa aaa cgt gcg gca agc gtt aaa gac gta tta aac gct ggc tgg aac   672
Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
    210                 215                 220

att aaa ggc gtt aaa ccc ggt aca aca gct tcc gat aac gtt gat ttc   720
Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
225                 230                 235                 240

gtc cgc act tac gac aca gtc gag ttc ttg agc gca gat acg aaa aca   768
Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
                245                 250                 255

acg act gtt aat gtg gaa agc aaa gac aac ggc aag aaa acc gaa gtt   816
Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
            260                 265                 270

aaa atc ggt gcg aag act tct gtt att aaa gaa aaa gac ggt aag ttg   864
Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
        275                 280                 285

gtt act ggt aaa gac aaa ggc gag aat ggt tct tct aca gac gaa ggc   912
Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
    290                 295                 300

gaa ggc tta gtg act gca aaa gaa gtg att gat gca gta aac aag gct   960
Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
305                 310                 315                 320
```

```
ggt tgg aga atg aaa aca aca acc gct aat ggt caa aca ggt caa gct   1008
Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
                325                 330                 335

gac aag ttt gaa acc gtt aca tca ggc aca aat gta acc ttt gct agt   1056
Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser
            340                 345                 350

ggt aaa ggt aca act gcg act gta agt aaa gat gat caa ggc aac atc   1104
Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
        355                 360                 365

act gtt atg tat gat gta aat gtc ggc gat gcc cta aac gtc aat cag   1152
Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
    370                 375                 380

ctg caa aac agc ggt tgg aat ttg gat tcc aaa gcg gtt gca ggt tct   1200
Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
385                 390                 395                 400

tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga aag atg   1248
Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
                405                 410                 415

gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att acc cgc   1296
Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
            420                 425                 430

aac ggt aaa aat atc gac atc gcc act tcg atg acc ccg cag ttt tcc   1344
Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
        435                 440                 445

agc gtt tcg ctc ggc gcg ggg gcg gat gcg ccc act ttg agc gtg gat   1392
Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
    450                 455                 460

ggg gac gca ttg aat gtc ggc agc aag aag gac aac aaa ccc gtc cgc   1440
Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg
465                 470                 475                 480

att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac gtc   1488
Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val
                485                 490                 495

gca caa ctt aaa ggc gtg gcg caa aac ttg aac aac cgc atc gac aat   1536
Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn
            500                 505                 510

gtg gac ggc aac gcg cgt gcg ggc atc gcc caa gcg att gca acc gca   1584
Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala
        515                 520                 525

ggt ctg gtt cag gcg tat ttg ccc ggc aag agt atg atg gcg atc ggc   1632
Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly
    530                 535                 540

ggc ggc act tat cgc ggc gaa gcc ggt tac gcc atc ggc tac tcc agt   1680
Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser
545                 550                 555                 560

att tcc gac ggc gga aat tgg att atc aaa ggc acg gct tcc ggc aat   1728
Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn
                565                 570                 575

tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat cag tgg taa   1776
```

```
Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
            580                 585                 590


<210> 21
<211> 591
<212> PRT
<213> Neisseria meningitidis

<400> 21
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
  1               5                  10                  15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
             20                  25                  30

Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
         35                  40                  45

Ala Ser Ala Asn Asn Glu Glu Gln Glu Glu Asp Leu Tyr Leu Asp Pro
     50                  55                  60

Val Gln Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
 65                  70                  75                  80

Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
                 85                  90                  95

Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
            100                 105                 110

Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
        115                 120                 125

Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
    130                 135                 140

Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
145                 150                 155                 160

Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
                165                 170                 175

Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
            180                 185                 190

Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
        195                 200                 205

Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
    210                 215                 220

Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
225                 230                 235                 240

Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
                245                 250                 255

Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
            260                 265                 270

Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
        275                 280                 285

Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
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290 295 300

Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
305 310 315 320

Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
325 330 335

Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser
340 345 350

Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
355 360 365

Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
370 375 380

Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
385 390 395 400

Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
405 410 415

Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
420 425 430

Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
435 440 445

Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
450 455 460

Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg
465 470 475 480

Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val
485 490 495

Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn
500 505 510

Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala
515 520 525

Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly
530 535 540

Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser
545 550 555 560

Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn
565 570 575

Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
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<210> 23
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oligonucleotide primer for PCR

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ccgatacgct gctgaata 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/01031

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07K 14/22; C12N 15/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int Cl[6]: C07K 14/22; C12N 15/31

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
As below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA) WPAT) Medline) Neisseria meningitidis adhesins TREMBL) GENPEPT) SWISS PROT PIR) Applicant's sequences

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VIRGI, M. Adv. in Exp. Med and Biol. 1996. 408: 113-122	ALL
A	RUDEL, T. et al. Nature 1995. 373: 357-359	ALL
A	VIRGI, M. et al. Mol Microbiol. 1992. 6(19): 2785-2795	ALL

☐ Further documents are listed in the continuation of Box C

☐ See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 1999	21 JAN 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **GILLIAN ALLEN** Telephone No.: (02) 6283 2266

Form PCT/ISA/210 (second sheet) (July 1998) cophin

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/01031

Box I **Observations where certain claims were f und unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect f certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: **(A) 2, 3, 5, 6, 7, 9; (B) 20(1) and 21**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

(A) Claims 2, 3, 5, 6, 7, 9 are not clear. They are essentially to polypeptides which have immunological activity against themselves or their parent organism (Neisseria meningitidis). This concept is virtually meaningless.

continued

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box BOX 1 (2)

Antigens do not display immunological activity against themselves, or the organism from which they derive. However, as far as I can determine, these claims are intended to encompass either:

(i) antigenic polypeptides or their encoding nucleic acids according to claims 1, 4 or 7, which provide protective immunity to an animal or human against Neisseria meningitidis infection, or

(ii) antibodies to such antigenic polypeptides.

Since these concepts are covered by other claims the lack of search on these claims does not affect the search coverage of the claims in toto.

(B) Claims 20(1) and 21 are to any antibodies against Neisseria meningitidis. They lack support from the description as they are not limited to antibodies to the polypeptides of the invention.